1. NAME OF THE MEDICINAL PRODUCT

Dobataf-3 (Dolutegravir, Emtricitabine and Tenofovir Alafenamide Tablets 50 mg / 200 mg / 25 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains Dolutegravir sodium equivalent to 50 mg of Dolutegravir, Emtricitabine 200 mg, Tenofovir Alafenamide 25 mg equivalent to 28 mg of Tenofovir Alafenamide Fumarate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM:

Film-coated tablet.

White to off-white colored, modified capsule shaped, film-coated tablets debossed with 'DET' on one side and plain on other side.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications

Treatment of HIV-1 Infection

Dolutegravir, emtricitabine and tenofovir alafenamide tablets is indicated as a complete regimen for the treatment of human immnunodeficiency virus 1 (HIV-1) infection in adults and pediatric patients weighing at least 25 kg.

Limitations of Use:

Dolutegravir, emtricitabine and tenofovir alafenamide tablets alone is not recommended in patients with resistance-associated integrase substitutions or clinically suspected integrase strand transfer inhibitor resistance because the dose of dolutegravir in dolutegravir, emtricitabine and tenofovir alafenamide tablets is insufficient in these subpopulations.

4.2 Posology and method of administration

Posology

Testing Prior to Initiation and During Treatment with Dolutegravir, Emtricitabine and Tenofovir Alafenamide Tablets

Pregnancy testing is recommended before initiation of dolutegravir, emtricitabine and tenofovir alafenamide tablets in adolescents and adults of childbearing potential.

Prior to or when initiating dolutegravir, emtricitabine and tenofovir alafenamide tablets, test patients for hepatitis B virus (HBV) infection.

Prior to initiation and during treatment with dolutegravir, emtricitabine and tenofovir alafenamide tablets, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus.

Recommended Dosage in Adults and Pediatric Patients Weighing at Least 25 kg (55 lbs)

Dolutegravir, emtricitabine and tenofovir alafenamide tablets is a three-drug fixed-dose combination product containing 50 mg of dolutegravir, 200 mg of emtricitabine (FTC) and 25 mg of tenofovir alafenamide (TAF). The recommended dosage of dolutegravir, emtricitabine and tenofovir alafenamide tablets is one tablet taken orally once daily with or without food in adults and pediatric patients weighing at least 25 kg (55 lbs) and creatinine clearance greater than or equal to 30 mL per minute.

The safety and effectiveness of dolutegravir, emtricitabine and tenofovir alafenamide tablets coadministered with an HIV-1 protease inhibitor that is administered with either ritonavir or cobicistat have not been established in pediatric subjects weighing less than 35 kg.

Not Recommended in Patients with Severe Renal Impairment

Dolutegravir, emtricitabine and tenofovir alafenamide tablets is not recommended in patients with estimated creatinine clearance below 30 mL per minute.

Not Recommended in Patients with Severe Hepatic Impairment

Dolutegravir, emtricitabine and tenofovir alafenamide tablets is not recommended in patients with severe hepatic impairment (Child-Pugh Score C).

Method of administration

Oral use.

One tablet (containing 50 mg of dolutegravir, 200 mg of emtricitabine and 25 mg of tenofovir alafenamide) taken once daily orally with or without regard to food.

4.3 Contraindications

Dolutegravir, emtricitabine and tenofovir alafenamide tablets is contraindicated in patients:

- with previous hypersensitivity reaction to dolutegravir or any of the components of this product *[see Warnings and Precautions (4.4)]*.
- receiving dofetilide due to the potential for increased dofetilide plasma concentrations and the risk for serious and/or life-threatening events with concomitant use of dolutegravir *[see Drug Interactions (4.5)]*.

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Severe Acute Exacerbation of Hepatitis B in Patients with HBV Infection

All patients should be tested for the presence of chronic hepatitis B virus (HBV) before or when initiating dolutegravir, emtricitabine and tenofovir alafenamide tablets.

Severe acute exacerbations of hepatitis B (e.g., liver decompensation and liver failure) have been reported in HBV-infected patients who have discontinued products containing dolutegravir, FTC and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of dolutegravir, emtricitabine and tenofovir alafenamide tablets. Patients infected with HBV who discontinue dolutegravir, emtricitabine and tenofovir alafenamide tablets should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, initiation of anti-hepatitis B therapy may be warranted, especially in patients with advanced liver disease or cirrhosis, since post-treatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure. HBV-uninfected patients should be offered vaccination.

Hypersensitivity Reactions

Hypersensitivity reactions have been reported with the use of dolutegravir, a component of dolutegravir, emtricitabine and tenofovir alafenamide tablets, and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury. The events were reported in less than 1% of subjects receiving dolutegravir in Phase 3 clinical trials. Discontinue dolutegravir, emtricitabine and tenofovir alafenamide tablets and other suspect agents immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters or peeling of the skin, oral blisters or lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema, difficulty breathing). Clinical status, including liver aminotransferases, should be monitored and appropriate therapy initiated. Delay in stopping treatment with dolutegravir, emtricitabine and

tenofovir alafenamide tablets or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction. Dolutegravir, emtricitabine and tenofovir alafenamide tablets is contraindicated in patients who have experienced a previous hypersensitivity reaction to dolutegravir or any of the components of this product.

Hepatotoxicity

Hepatic adverse events have been reported in patients receiving a dolutegravir-containing regimen. Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of dolutegravir, emtricitabine and tenofovir alafenamide tablets. In some cases, the elevations in transaminases were consistent with immune reconstitution syndrome or hepatitis B reactivation particularly in the setting where anti-hepatitis therapy was withdrawn. Cases of hepatic toxicity, including elevated serum liver biochemistries, hepatitis, and acute liver failure have been reported in patients receiving a dolutegravir-containing regimen without pre-existing hepatic disease or other identifiable risk factors. Drug-induced liver injury leading to liver transplant has been reported with fixed-dose abacavir, dolutegravir, and lamivudine. Monitoring for hepatotoxicity is recommended.

Embryo-Fetal Toxicity

An ongoing observational study showed an association between dolutegravir, a component of dolutegravir, emtricitabine and tenofovir alafenamide tablets, and an increased risk of neural tube defects when dolutegravir was administered at the time of conception and in early pregnancy. As there is limited understanding of the association of reported types of neural tube defects with dolutegravir use, inform adolescents and adults of childbearing potential, including those actively trying to become pregnant, about the potential increased risk of neural tube defects with dolutegravir, emtricitabine and tenofovir alafenamide tablets. Assess the risks and benefits of dolutegravir, emtricitabine and tenofovir alafenamide tablets and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy or if pregnancy is confirmed in the first trimester.

Pregnancy testing is recommended before initiation of dolutegravir, emtricitabine and tenofovir alafenamide tablets in adolescents and adults of childbearing potential.

Adolescents and adults of childbearing potential should be counselled on the consistent use of effective contraception.

Dolutegravir, emtricitabine and tenofovir alafenamide tablets may be considered during the second and third trimesters of pregnancy if the expected benefit justifies the potential risk to the pregnant woman and the fetus.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in HIV-1 infected patients treated with combination antiretroviral therapy, including dolutegravir, a component of emtricitabine and tenofovir alafenamide. During the initial phase of combination antiretroviral treatment, HIV-1 infected 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.

Autoimmune disorders (such as Graves' disease, polymyositis, Guillain-Barré syndrome, and autoimmune hepatitis) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment.

Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions

The concomitant use of dolutegravir, emtricitabine and tenofovir alafenamide tablets and other drugs may result in known or potentially significant drug interactions, some of which may lead to:

- Loss of therapeutic effect of dolutegravir, emtricitabine and tenofovir alafenamide tablets and possible development of resistance.
- Possible clinically significant adverse reactions from greater exposures of concomitant drugs.

For concomitant drugs for which the interaction can be mitigated, please see Table 4 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during therapy with dolutegravir, emtricitabine and tenofovir alafenamide tablets; review concomitant medications during therapy with dolutegravir, emtricitabine and tenofovir alafenamide tablets; and monitor for the adverse reactions associated with the concomitant drugs.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in HIV-1 infected patients treated with combination antiretroviral therapy, including dolutegravir and FTC, two components of dolutegravir, emtricitabine and tenofovir alafenamide tablets. During the initial phase of combination antiretroviral treatment, HIV-1 infected 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.

Autoimmune disorders (such as Graves' disease, polymyositis, Guillain-Barré syndrome, and autoimmune hepatitis) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment.

New Onset or Worsening Renal Impairment

Postmarketing cases of renal impairment, including acute renal failure, proximal renal tubulopathy (PRT), and Fanconi syndrome have been reported with TAF-containing products; while most of these cases were characterized by potential confounders that may have contributed to the reported renal events, it is also possible these factors may have predisposed patients to tenofovir-related adverse events.

Dolutegravir, emtricitabine and tenofovir alafenamide tablets is not recommended in patients with estimated creatinine clearance below 30 mL per minute because data in this population are insufficient.

Patients taking tenofovir prodrugs who have impaired renal function and those taking nephrotoxic agents including non-steroidal anti-inflammatory drugs are at increased risk of developing renal-related adverse reactions.

Prior to or when initiating dolutegravir, emtricitabine and tenofovir alafenamide tablets, and during treatment with dolutegravir, emtricitabine and tenofovir alafenamide tablets on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus. Discontinue dolutegravir, emtricitabine and tenofovir alafenamide tablets in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

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, including FTC, a component dolutegravir, of emtricitabine and tenofovir alafenamide tablets, and tenofovir DF, another prodrug of tenofovir, alone or in combination with other antiretrovirals. Treatment with dolutegravir, emtricitabine and tenofovir alafenamide tablets 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).

Pediatric Use

The safety and effectiveness of dolutegravir, emtricitabine and tenofovir alafenamide tablets for the treatment of HIV-1 infection in pediatric patients weighing at least 25 kg was established through studies with the individual components. Dolutegravir, emtricitabine and tenofovir alafenamide tablets is a fixed-dose combination product which cannot be adjusted for pediatric patients weighing less than 25 kg.

The safety and effectiveness of dolutegravir, emtricitabine and tenofovir alafenamide tablets coadministered with an HIV-1 protease inhibitor that is administered with either ritonavir or cobicistat have not been established in pediatric subjects weighing less than 35 kg.

Geriatric Use

Dolutegravir

Clinical trials of dolutegravir did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration of dolutegravir in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

FTC and TAF

In clinical trials, 80 of the 97 subjects enrolled aged 65 years and over received FTC+TAF and EVG+COBI. No differences in safety or efficacy have been observed between elderly subjects and adults between 18 and less than 65 years of age.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of Dolutegravir on the Pharmacokinetics of Other Agents

In vitro, dolutegravir inhibited the renal organic cation transporters, OCT2 (IC_{50} = 1.93 microM) and multidrug and toxin extrusion transporter (MATE) 1 (IC_{50} = 6.34 microM). *In vivo*, dolutegravir inhibits tubular secretion of creatinine by inhibiting OCT2 and potentially MATE1. Dolutegravir may increase plasma concentrations of drugs eliminated via OCT2 or MATE1 (dofetilide, dalfampridine, and metformin, Table 1).

In vitro, dolutegravir inhibited the basolateral renal transporters, organic anion transporter (OAT) 1 (IC_{50} = 2.12 microM) and OAT3 (IC_{50} = 1.97 microM). However, *in vivo*, dolutegravir did not alter the plasma concentrations of tenofovir or para-amino hippurate, substrates of OAT1 and OAT3.

In vitro, dolutegravir did not inhibit (IC_{50} greater than 50 microM) the following: cytochrome P450 (CYP) 1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, uridyl diphosphate glucuronosyl transferase (UGT)1A1, UGT2B7, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), bile salt export pump (BSEP), organic anion transporter polypeptide (OATP)1B1, OATP1B3, OCT1, multidrug resistance protein (MRP)2, or MRP4. *In vitro*, dolutegravir did not induce CYP1A2, CYP2B6, or CYP3A4. Based on these data and the results of drug interaction trials, dolutegravir is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or transporters.

Effect of Other Agents on the Pharmacokinetics of Dolutegravir, FTC, or TAF

Dolutegravir

Dolutegravir, one component of dolutegravir, emtricitabine and tenofovir alafenamide tablets, is metabolized by UGT1A1 with some contribution from CYP3A. Dolutegravir is also a substrate of UGT1A3, UGT1A9, BCRP, and P-gp *in vitro*. Drugs that induce those enzymes and transporters may decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir.

Coadministration of dolutegravir and other drugs that inhibit these enzymes may increase dolutegravir plasma concentration.

Etravirine significantly reduced plasma concentrations of dolutegravir, but the effect of etravirine was mitigated by coadministration of lopinavir/ritonavir or darunavir/ritonavir, and is expected to be mitigated by atazanavir/ritonavir (Table 1).

In vitro, dolutegravir was not a substrate of OATP1B1 or OATP1B3.

FTC and TAF

TAF, one component of dolutegravir, emtricitabine and tenofovir alafenamide tablets, is a substrate of P-gp, BCRP, OATP1B1, and OATP1B3. Drugs that strongly affect P-gp and BCRP activity may lead to changes in TAF absorption (see Table 4). Drugs that induce P-gp activity are expected to decrease the absorption of TAF, resulting in decreased plasma concentration of TAF, which may lead to loss of therapeutic effect of dolutegravir, emtricitabine and tenofovir alafenamide tablets and development of resistance. Coadministration of dolutegravir, emtricitabine and tenofovir alafenamide tablets with other drugs that inhibit P-gp and BCRP may increase the absorption and plasma concentration of TAF. TAF is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or UGT1A1. TAF is a weak inhibitor of CYP3A *in vitro*. TAF is not an inhibitor or inducer of CYP3A *in vivo*.

Established and Other Potentially Significant Drug Interactions

There were no drug interaction trials conducted with dolutegravir and fixed-dose emtricitabine and tenofovir alafenamide or with the fixed-dose combination of all three components.

Information regarding potential drug interactions with dolutegravir, emtricitabine and tenofovir alafenamide (Table 4) are provided below.

These recommendations are based on either drug interaction trials or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy.

Table 1 Established and Other Potentially Significant Drug Interactions for Dolutegravir, Emtricitabine and Tenofovir Alafenamide: Alterations in Dose May Be Recommended Based on Drug Interaction Trials or Predicted Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir, TAF and/or Concomitant Drug	Clinical Comment
HIV-1 Antiviral Agents		
Non-nucleoside reverse transcriptase inhibitor: Etravirine[a]	↓ Dolutegravir	Use of dolutegravir, emtricitabine and tenofovir alafenamide tablets with etravirine without coadministration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir is not recommended.
Non-nucleoside reverse transcriptase inhibitor: Efavirenz[a]	↓ Dolutegravir	If coadministration with efavirenz is necessary, an additional 50 mg dose of dolutegravir should be taken, separated by 12 hours from dolutegravir, emtricitabine and tenofovir alafenamide tablets.
Non-nucleoside reverse transcriptase inhibitor: Nevirapine	↓ Dolutegravir	Avoid coadministration with dolutegravir, emtricitabine and tenofovir alafenamide tablets because there are insufficient data to make dosing recommendations.
Protease inhibitors: Fosamprenavir/ritonavir[a]	↓ Dolutegravir	If coadministration with fosamprenavir/ritonavir is necessary, an additional 50 mg dose of dolutegravir should be taken, separated by 12 hours from dolutegravir, emtricitabine and tenofovir alafenamide tablets
Tipranavir/ritonavir	↓ Dolutegravir ↓ TAF	Coadministration with dolutegravir, emtricitabine and tenofovir alafenamide tablets is not recommended because of the TAF component.
Other Agents		
Antiarrhythmics: Dofetilide	↑ Dolutegravir	Coadministration is contraindicated with dolutegravir, emtricitabine and tenofovir alafenamide tablets *[see Contraindications (4)]*.
Antimycobacterials: Rifabutin Rifapentine	↓ TAF	Coadministration of dolutegravir, emtricitabine and tenofovir alafenamide tablets with rifabutin or rifapentine is not recommended.
Rifampin[a]	↓ Dolutegravir ↓ TAF	Coadministration of dolutegravir, emtricitabine and tenofovir alafenamide tablets with rifampin is not recommended because of the TAF component.

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir, TAF and/or Concomitant Drug	Clinical Comment
Anticonvulsants: Carbamazepine[a]	↓ Dolutegravir ↓ TAF	Consider alternative anticonvulsant. If coadministration with carbamazepine is necessary, an additional 50 mg dose of dolutegravir should be taken, separated by 12 hours from dolutegravir, emtricitabine and tenofovir alafenamide tablets.
Oxcarbazepine Phenytoin Phenobarbital	↓ Dolutegravir ↓ TAF	Avoid coadministration with dolutegravir, emtricitabine and tenofovir alafenamide tablets because there are insufficient data to make dosing recommendations.
Anti-diabetic medications: Metformin[a]	↑ Metformin	Refer to the prescribing information of metformin for assessing the benefit and risk of concomitant use with metformin.
Herbal Products: St. John's wort *(Hypericum perforatum)*	↓ Dolutegravir ↓ TAF	Avoid coadministration with dolutegravir, emtricitabine and tenofovir alafenamide tablets because there are insufficient data to make dosing recommendations.
Medications containing polyvalent cations (e.g., Mg or Al): Cation-containing antacids[a] or laxatives Sucralfate Buffered medications	↓ Dolutegravir	Administer dolutegravir, emtricitabine and tenofovir alafenamide tablets 2 hours before or 6 hours after taking medications containing polyvalent cations.
Oral calcium or iron supplements, including multivitamins containing calcium or iron[a]	↓ Dolutegravir	When taken with food, dolutegravir, emtricitabine and tenofovir alafenamide tablets and supplements or multivitamins containing calcium or iron can be taken at the same time. Under fasting conditions, dolutegravir, emtricitabine and tenofovir alafenamide tablets should be taken 2 hours before or 6 hours after taking supplements containing calcium or iron.
Potassium channel blockers: Dalfampridine	↑ Dalfampridine	Elevated levels of dalfampridine increase the risk of seizures. The potential benefits of taking dalfampridine concurrently with dolutegravir, emtricitabine and tenofovir alafenamide tablets should be considered against the risk of seizures in these patients.

Drugs without Clinically Significant Interactions with Dolutegravir, FTC, and TAF

Based on drug interaction trial results, the following drugs can be coadministered with dolutegravir without a dose adjustment: atazanavir/ritonavir, darunavir/ritonavir, daclatasvir, elbasvir/grazoprevir, methadone, midazolam, omeprazole, oral contraceptives containing norgestimate and ethinyl estradiol, prednisone, rifabutin, rilpivirine, sofosbuvir/velpatasvir, and tenofovir.

Based on drug interaction studies conducted with the components of emtricitabine and tenofovir alafenamide, no clinically significant drug interactions have been either observed or are expected when emtricitabine and tenofovir alafenamide is combined with the following antiretroviral agents: atazanavir with ritonavir or cobicistat, darunavir with ritonavir or cobicistat, dolutegravir, efavirenz, ledipasvir, lopinavir/ritonavir, maraviroc, nevirapine, raltegravir, rilpivirine, and sofosbuvir. No clinically significant drug interactions have been either observed or are expected when emtricitabine and tenofovir alafenamide is combined with the following drugs: buprenorphine, itraconazole, ketoconazole, lorazepam, methadone, midazolam, naloxone, norbuprenorphine, norgestimate/ethinyl estradiol, and sertraline.

Drugs Affecting Renal Function

Because FTC and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, coadministration of dolutegravir, emtricitabine and tenofovir alafenamide tablets with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of FTC, tenofovir, and other renally eliminated drugs and this may increase the risk of adverse reactions. Some examples of drugs that are eliminated by active tubular secretion include, but are not limited to, acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs *[see Warnings and Precautions (4.4)]*.

4.6 Fertility, pregnancy and lactation

Pregnancy

Data from an ongoing birth outcome surveillance study has identified an increased risk of neural tube defects when dolutegravir, a component of dolutegravir, emtricitabine and tenofovir alafenamide tablets, is administered at the time of conception. As defects related to closure of the neural tube occur from conception through the first 6 weeks of gestation, embryos exposed to dolutegravir from the time of conception through the first 6 weeks of gestation are at potential risk.

Advise adolescents and adults of childbearing potential, including those actively trying to become pregnant, of the potential risk of neural tube defects with the use of dolutegravir, emtricitabine and tenofovir alafenamide tablets. Assess the risks and benefits of dolutegravir, emtricitabine and tenofovir alafenamide tablets and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy or if pregnancy is confirmed in the first trimester. A benefit-risk assessment should consider factors such as feasibility of switching to another antiretroviral regimen, tolerability, ability to maintain viral suppression, and risk of HIV-1 transmission to the infant against the risk of neural tube defects associated with in utero dolutegravir exposure during critical periods of fetal development *[see Warnings and Precautions (4.4)]*.

There are insufficient human data on the use of dolutegravir, emtricitabine and tenofovir alafenamide tablets during pregnancy to definitively assess a drug-associated risk of birth defects and miscarriage. The background risk for major birth defects for the indicated population is unknown. In the U.S. general population, the estimated background rate for major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

In animal reproduction studies, no evidence of adverse developmental outcomes was observed with dolutegravir at systemic exposures (AUC) less than (rabbits) and approximately 27 times (rats) the exposure in humans at the maximum recommended human dose (MRHD) of dolutegravir *(see Data)*. No adverse developmental effects were observed when FTC and TAF were administered separately during the period of organogenesis at exposures 60 and 108 times (mice and rabbits, respectively) the FTC exposure and at exposure equal to or 53 times (rats and rabbits, respectively) the TAF exposure at the recommended daily dose of FTC and TAF *[see Data]*. Likewise, no adverse developmental effects were seen when FTC was administered to mice through lactation at exposures up to approximately 60 times the exposure at the recommended daily dose of FTC. No adverse effects were observed in the offspring when TDF was administered through lactation at tenofovir exposures of approximately 14 times the exposure at the recommended daily dosage of TAF.

Breast-feeding

The Centers for Disease Control and Prevention recommends that HIV-1-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection.

Dolutegravir is present in human milk. It is not known whether dolutegravir affects human milk production or has effects on the breastfed infant.

Based on limited data, FTC has been shown to be present in human breast milk; it is not known if TAF is present in human breast milk. Tenofovir has been shown to be present in the milk of lactating rats and rhesus monkeys after administration of TDF. It is not known if TAF is present in animal milk.

It is not known if dolutegravir, emtricitabine and tenofovir alafenamide tablets affects milk production or has effects on the breastfed child.

Because of the potential for: 1) HIV-1 transmission (in HIV-negative infants); 2) developing viral resistance (in HIV-positive infants); and 3) adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are receiving dolutegravir, emtricitabine and tenofovir alafenamide tablets.

Fertility

In adolescents and adults of childbearing potential currently on dolutegravir, emtricitabine and tenofovir alafenamide tablets who are actively trying to become pregnant or if pregnancy is confirmed in the first trimester, assess the risks and benefits of continuing dolutegravir, emtricitabine and tenofovir alafenamide tablets and discuss with the patient if an alternative treatment should be considered.

Pregnancy Testing

Pregnancy testing is recommended in adolescents and adults of childbearing potential before initiation of dolutegravir, emtricitabine and tenofovir alafenamide tablets.

Contraception

Adolescents and adults of childbearing potential who are taking dolutegravir, emtricitabine and tenofovir alafenamide tablets should be counselled on the consistent use of effective contraception.

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, dizziness has been reported during treatment with Dolutegravir, Emtricitabine and Tenofovir Alafenamide. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving and operating machinery.

4.8 Undesirable effects

The following serious adverse drug reactions are discussed in sections 4.4 Special warnings and precautions for use:

- Severe Acute Exacerbation of Hepatitis B.
- Hypersensitivity reactions.
- Hepatotoxicity.
- Immune Reconstitution Syndrome.
- New Onset or Worsening Renal Impairment.
- Lactic Acidosis/Severe Hepatomegaly with Steatosis.

The adverse drug reactions considered at least possibly related to dolutegravir, Emtricitabine and Tenofovir Alafenamide are listed by system organ class.

Gastrointestinal Disorders: Abdominal pain, abdominal discomfort, flatulence, upper abdominal pain, vomiting.

Hepatobiliary Disorders: Hepatitis.

Musculoskeletal Disorders: Myositis.

Psychiatric Disorders: Suicidal ideation, attempt, behavior, or completion. These events were observed primarily in subjects with a pre-existing history of depression or other psychiatric illness.

Renal and Urinary Disorders: Renal impairment.

Skin and Subcutaneous Tissue Disorders: Pruritus.

Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postmarketing use. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Dolutegravir

Hepatobiliary Disorders

Acute liver failure, hepatotoxicity.

Investigations

Weight increased.

Musculoskeletal

Arthralgia, myalgia.

Psychiatric

Anxiety

TAF

Skin and Subcutaneous Tissue Disorders

Angioedema, urticaria, and rash.

Renal and Urinary Disorders

Acute renal failure, acute tubular necrosis, proximal renal tubulopathy, and Fanconi syndrome.

4.9 Overdose

There is no known specific treatment for overdose with dolutegravir, emtricitabine and tenofovir alafenamide tablets. If overdose occurs, the patient should be monitored, and standard supportive treatment applied as required.

Dolutegravir

As dolutegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

FTC and TAF

Limited clinical experience is available at doses higher than the recommended dose of FTC. In one clinical pharmacology study, single doses of FTC 1,200 mg (6 times the recommended dose of FTC) were administered to 11 subjects. No severe adverse reactions were reported. The effects of higher doses are not known.

Hemodialysis treatment removes approximately 30% of the FTC dose over a 3-hour dialysis period starting within 1.5 hours of FTC dosing (blood flow rate of 400 mL per minute and a dialysate flow rate of 600 mL per minute). It is not known whether FTC can be removed by peritoneal dialysis.

TAF

Limited clinical experience is available at doses higher than the recommended dose of TAF. A single dose of 125 mg TAF (5 times the TAF dose in 200 mg/25 mg fixed-dose emtricitabine and tenofovir alafenamide) was administered to 48 healthy subjects; no serious adverse reactions were reported. The effects of higher doses are unknown. Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of Action

Dolutegravir, emtricitabine and tenofovir alafenamide tablets is a fixed-dose combination of the HIV-1 antiretroviral drugs dolutegravir, FTC and TAF.

Dolutegravir

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. Strand transfer biochemical assays using purified HIV-1 integrase and pre-processed substrate DNA resulted in IC_{50} values of 2.7 nM and 12.6 nM.

Emtricitabine and Tenofovir alafenamide

Emtricitabine: FTC, a synthetic nucleoside analog of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 reverse transcriptase by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5'-triphosphate is a weak inhibitor of mammalian DNA polymerases α, β, ε, and mitochondrial DNA polymerase γ.

Tenofovir Alafenamide: TAF is a phosphonoamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analog). Plasma exposure to TAF allows for permeation into cells and then TAF is intracellularly converted to tenofovir through hydrolysis by cathepsin A. Tenofovir is subsequently phosphorylated by cellular kinases to the active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV-1 replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain-termination.

5.2 Pharmacokinetic properties

Absorption, Distribution, Metabolism and Excretion

Dolutegravir

The pharmacokinetic (PK) properties of dolutegravir have been evaluated in healthy adult subjects and HIV-1–infected adult subjects and are provided in Table 2. Exposure to dolutegravir was generally similar between healthy subjects and HIV-1–infected subjects.

Table 1. Dolutegravir Steady-State Pharmacokinetic Parameter Estimates in HIV–1–Infected Adults

Parameter	50 mg Once Daily Geometric Mean[a] (%CV)
$AUC_{(0\text{-}24)}$ (mcg.h/mL)	53.6 (27)
C_{max} (mcg/mL)	3.67 (20)
C_{min} (mcg/mL)	1.11 (46)

[a] Based on population pharmacokinetic analyses using data from SPRING-1 and SPRING-2.

Following oral administration of dolutegravir, peak plasma concentrations were observed 1 to 3 hours postdose. With once-daily dosing, PK steady state is achieved within approximately 5 days with average accumulation ratios for AUC, C_{max}, and C_{24h} ranging from 1.2 to 1.5.

Dolutegravir is a P-gp substrate *in vitro*. The absolute bioavailability of dolutegravir has not been established.

Dolutegravir may be taken with or without food. Food increased the extent of absorption and slowed the rate of absorption of dolutegravir. Low-, moderate-, and high-fat meals increased dolutegravir $AUC_{(0-\infty)}$ by 33%, 41%, and 66%; increased C_{max} by 46%, 52%, and 67%; and prolonged T_{max} to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively.

Dolutegravir is highly bound (greater than or equal to 98.9%) to human plasma proteins based on *in vivo* data and binding is independent of plasma concentration of dolutegravir. The apparent volume of distribution (Vd/F) following 50 mg once-daily administration is estimated at 17.4 L based on a population PK analysis.

Cerebrospinal Fluid (CSF): In 12 treatment-naïve subjects on dolutegravir 50 mg daily plus abacavir/lamivudine, the median dolutegravir concentration in CSF was 13.2 ng per mL (range: 3.74 ng per mL to 18.3 ng per mL) 2 to 6 hours postdose after 16 weeks of treatment. The clinical relevance of this finding has not been established.

Dolutegravir has a terminal half-life of approximately 14 hours and an apparent clearance (CL/F) of 1.0 L per hour based on population PK analyses.

Dolutegravir is primarily metabolized via UGT1A1 with some contribution from CYP3A.

In a meta-analysis of healthy subject trials, subjects with UGT1A1 (n = 7) genotypes conferring poor dolutegravir metabolism had a 32% lower clearance of dolutegravir and 46% higher AUC compared with subjects with genotypes associated with normal metabolism via UGT1A1 (n = 41).

After a single oral dose of [^{14}C] dolutegravir, 53% of the total oral dose was excreted unchanged in feces. Thirty-one percent of the total oral dose was excreted in urine, represented by an ether glucuronide of dolutegravir (18.9% of total dose), a metabolite formed by oxidation at the benzylic carbon (3.0% of total dose), and its hydrolytic N-dealkylation product (3.6% of total dose). Renal elimination of unchanged drug was low (less than 1% of the dose).

FTC and TAF

The PK properties of the components of fixed-dose emtricitabine and tenofovir alafenamide are provided in Table 2. The multiple dose PK parameters of FTC and TAF and its metabolite tenofovir are provided in Table 3.

Table 2 Pharmacokinetic Properties of the Components of Fixed-Dose Emtricitabine and Tenofovir Alafenamide

	Emtricitabine	Tenofovir Alafenamide
Absorption		
T_{max} (h)	3	1
Effect of high fat meal (relative to fasting)[a]	AUC Ratio = 0.91 (0.89, 0.93) C_{max} Ratio = 0.74 (0.69, 0.78)	AUC Ratio = 1.75 (1.64, 1.88) C_{max} Ratio= 0.85 (0.75, 0.95)
Distribution		
% Bound to human plasma proteins	<4	~80
Source of protein binding data	*In vitro*	*Ex vivo*
Blood-to-plasma ratio	0.6	1.0
Metabolism		
Metabolism	Not significantly metabolized	Cathepsin A[b] (PBMCs) CES1 (hepatocytes) CYP3A (minimal)
Elimination		
Major route of elimination	Glomerular filtration and active tubular secretion	Metabolism (>80% of oral dose)
$t_{1/2}$ (h)[c]	10	0.51
% Of dose excreted in urine[d]	70	<1
% Of dose excreted in feces[d]	13.7	31.7

PBMCs=peripheral blood mononuclear cells; CES1=carboxylesterase 1

[a.] Values refer to geometric mean ratio [High-fat meal/ fasting] in PK parameters and (90% confidence interval). High-calorie/high-fat meal = ~800 kcal, 50% fat.

[b.] *In vivo*, TAF is hydrolyzed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite, tenofovir diphosphate. *In vitro* studies have shown that TAF is metabolized to tenofovir by cathepsin A in PBMCs and macrophages; and by CES1 in hepatocytes. Upon coadministration with the moderate CYP3A inducer probe efavirenz, TAF exposure was unaffected.

[c.] $t_{1/2}$ values refer to median terminal plasma half-life. Note that the pharmacologically active metabolite, tenofovir diphosphate, has a half-life of 150 to 180 hours within PBMCs.

[d.] Dosing in mass balance studies: FTC (single dose administration of [^{14}C] emtricitabine after multiple dosing of emtricitabine for 10 days); TAF (single dose administration of [^{14}C] tenofovir alafenamide).

Table 3 Multiple Dose PK Parameters of Emtricitabine, Tenofovir Alafenamide and its Metabolite Tenofovir Following Oral Administration with Food in HIV-Infected Adults

Parameter Mean (CV%)	Emtricitabine[a]	Tenofovir Alafenamide[b]	Tenofovir[c]
C_{max} (microgram per mL)	2.1 (20.2)	0.16 (51.1)	0.02 (26.1)
AUC_{tau} (microgram•hour per mL)	11.7 (16.6)	0.21 (71.8)	0.29 (27.4)
C_{trough} (microgram per mL)	0.10 (46.7)	NA	0.01 (28.5)

CV=Coefficient of Variation; NA=Not Applicable

[a.] From Intensive PK analysis in a phase 2 trial in HIV-infected adults treated with FTC+TAF and EVG+COBI.

[b.] From Population PK analysis in two trials of treatment-naïve adults with HIV-1 infection treated with FTC+TAF with EVG+COBI (N=539).

[c.] From Population PK analysis in two trials of treatment-naïve adults with HIV-1 infection treated with FTC+TAF with EVG+COBI (N=841).

Effects of Food on Oral Absorption of Dolutegravir, Emtricitabine and Tenofovir Alafenamide

Food is unlikely to have a clinically meaningful effect on systemic exposures of dolutegravir, emtricitabine, and tenofovir, following drug administration.

Specific Populations

Pediatric Patients: Dolutegravir, emtricitabine and tenofovir alafenamide tablets is a fixed-dose combination product which cannot be adjusted for patients weighing less than 25 kg (55 lbs).

Dolutegravir: The pharmacokinetics of dolutegravir were evaluated in the IMPAACT P1093 trial and in 2 weight-band-based PK substudies from the ODYSSEY trial.

Mean dolutegravir AUC_{0-24h} and C24h in HIV-1–infected pediatric subjects were comparable to those in adults after 50 mg once daily or 50 mg twice daily.

FTC and TAF: Exposures of FTC and TAF achieved in 23 pediatric subjects between the ages of 6 to less than 12 years and weighing at least 25 kg (55 lbs) who received FTC+TAF with EVG+COBI were higher (20% to 80% for AUC) than exposures achieved in adults following the administration of this dosage regimen; however, the increase was not considered clinically significant (Table 4).

Table 4: Multiple Dose PK Parameters of Emtricitabine, Tenofovir Alafenamide and its Metabolite Tenofovir Following Oral Administration of FTC+TAF with EVG+COBI in HIV-Infected Pediatric Subjects Aged 6 to less than 12 Years[a]

Parameter Mean (CV%)	Emtricitabine	Tenofovir Alafenamide	Tenofovir
C_{max} (microgram per mL)	3.4 (27.0)	0.31 (61.2)	0.03 (20.8)
AUC_{tau} (microgram•hour per mL)	20.6[b] (18.9)	0.33 (44.8)	0.44 (20.9)
C_{trough} (microgram per mL)	0.11 (24.1)	NA	0.02 (24.9)

CV = Coefficient of Variation; NA = Not Applicable

[a]From Intensive PK analysis in a trial in virologically-suppressed pediatric subjects with HIV-1 infection (N=23).

Mean exposures of TAF in 24 pediatric subjects aged 12 to less than 18 years who received FTC+TAF with EVG+COBI were decreased (23% for AUC) and FTC exposures were similar compared to exposures achieved in treatment-naïve adults following administration of this dosage regimen. The TAF exposure differences are not thought to be clinically significant based on exposure-response relationships (Table 5).

Table 5 Multiple Dose PK Parameters of Emtricitabine, Tenofovir Alafenamide, and its Metabolite Tenofovir Following Oral Administration of FTC+TAF with EVG+COBI in HIV-Infected Pediatric Subjects Aged 12 to less than 18 Years[a]

Parameter Mean (CV%)	Emtricitabine	Tenofovir Alafenamide	Tenofovir
C_{max} (microgram per mL)	2.3 (22.5)	0.17 (64.4)	0.02 (23.7)
AUC_{tau} (microgram•hour per mL)	14.4 (23.9)	0.20[b] (50.0)	0.29[b] (18.8)
C_{trough} (microgram per mL)	0.10[b] (38.9)	NA	0.01 (21.4)

CV = Coefficient of Variation; NA = Not Applicable

[a.] From Intensive PK analysis in a trial in treatment-naïve pediatric subjects with HIV-1 infection (N=24).

[b.] N=23

Geriatric Patients

Dolutegravir: Population pharmacokinetic analysis indicated age had no clinically relevant effect on the pharmacokinetics of dolutegravir.

FTC and TAF: Pharmacokinetics of FTC and TAF have not been fully evaluated in the elderly (65 years of age and older). Population pharmacokinetics analysis of HIV-infected subjects in Phase 2 and Phase 3 trials of FTC + TAF and EVG + COBI showed that age did not have a clinically relevant effect on exposures of TAF up to 75 years of age.

Patients with Renal Impairment

Dolutegravir, emtricitabine and tenofovir alafenamide tablets are not recommended for patients with severe renal impairment (estimated creatinine clearance below 30 mL per min) because dolutegravir, emtricitabine and tenofovir alafenamide tablets is a fixed-dose combination product and the dosage of the individual components cannot be adjusted.

Patients with Hepatic Impairment

Dolutegravir: Dolutegravir is primarily metabolized and eliminated by the liver. In a trial comparing 8 subjects with moderate hepatic impairment (Child-Pugh Class B) with 8 matched healthy controls, exposure of dolutegravir from a single 50 mg dose was similar between the 2 groups. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of dolutegravir has not been studied.

FTC: The pharmacokinetics of FTC has not been studied in subjects with hepatic impairment; however, FTC is not significantly metabolized by liver enzymes, so the impact of hepatic impairment should be limited.

TAF: Clinically relevant changes in tenofovir pharmacokinetics in subjects with hepatic impairment were not observed in subjects with mild to moderate (Child-Pugh Class A and B) hepatic impairment.

Hepatitis B Virus (HBV) and/or Hepatitis C Virus (HCV) Co-infection

Dolutegravir: Population analyses using pooled PK data from adult trials indicated no clinically relevant effect of HCV co-infection on the pharmacokinetics of dolutegravir. There were limited data on HBV co-infection.

FTC and TAF: The pharmacokinetics of FTC and TAF have not been fully evaluated in subjects infected with hepatitis B and/or C virus.

Gender and Race

Dolutegravir: Population analyses using pooled pharmacokinetic data from adult trials indicated gender and race had no clinically relevant effect on the exposure of dolutegravir.

FTC and TAF: Based on population pharmacokinetic analyses, there are no clinically meaningful differences based on race or gender.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Dolutegravir

Two-year carcinogenicity studies in mice and rats were conducted with dolutegravir. Mice were administered doses of up to 500 mg per kg, and rats were administered doses of up to 50 mg per kg. In mice, no significant increases in the incidence of drug-related neoplasms were observed at the highest doses tested, resulting in dolutegravir AUC exposures approximately 14 times higher than those in humans at a dose of 50 mg twice daily. In rats, no increases in the incidence of drug-related neoplasms were observed at the highest dose tested, resulting in dolutegravir AUC exposures 10 times and 15 times higher in males and females, respectively, than those in humans at a dose of 50 mg twice daily.

Emtricitabine

In long-term carcinogenicity studies of FTC, no drug-related increases in tumor incidence were found in mice at doses up to 750 mg per kg per day (23 times the human systemic exposure at the recommended dose of 200 mg per day in emtricitabine and tenofovir alafenamide) or in rats at doses up to 600 mg per kg per day (28 times the human systemic exposure at the recommended dose in emtricitabine and tenofovir alafenamide).

Tenofovir Alafenamide

Since TAF is rapidly converted to tenofovir and a lower tenofovir exposure in rats and mice was observed after TAF administration compared to TDF administration, carcinogenicity studies were conducted only with TDF. Long-term oral carcinogenicity studies of TDF in mice and rats were carried out at exposures up to approximately 10 times (mice) and 4 times (rats) those observed in humans at the recommended dose of TDF (300 mg) for HIV-1 infection. The tenofovir exposure in these studies was approximately 167 times (mice) and 55 times (rat) those observed in humans after administration of the daily recommended dose of emtricitabine and tenofovir alafenamide. At the high dose in female mice, liver adenomas were increased at tenofovir exposures approximately 10 times (300 mg TDF) and 167 times (emtricitabine and tenofovir alafenamide) the exposure observed in humans. In rats, the study was negative for carcinogenic findings.

Mutagenesis

Dolutegravir

Dolutegravir was not genotoxic in the bacterial reverse mutation assay, mouse lymphoma assay, or in the *in vivo* rodent micronucleus assay.

Emtricitabine

FTC was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or mouse micronucleus assays.

Tenofovir Alafenamide

TAF was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or rat micronucleus assays.

Impairment of Fertility

Dolutegravir

In a study conducted in rats, there were no effects on mating or fertility with dolutegravir up to 1,000 mg per kg per day. This dose is associated with an exposure that is approximately 24 times higher than the exposure in humans at a dose of 50 mg twice daily.

Emtricitabine

FTC did not affect fertility in male rats at approximately 140 times or in male and female mice at approximately 60 times higher exposures (AUC) than in humans given the recommended 200 mg daily dosage in emtricitabine and tenofovir alafenamide. Fertility was normal in the offspring of mice exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 60 times higher than human exposures at the recommended 200 mg daily dosage in emtricitabine and tenofovir alafenamide.

Tenofovir Alafenamide

There were no effects on fertility, mating performance, or early embryonic development when TAF was administered to male rats at a dose equivalent to 62 times (25 mg TAF) the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 14 days prior to mating through Day 7 of gestation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:

Mannitol, Microcrystalline Cellulose, Povidone, Ferric Oxide, Sodium Starch Glycolate, Sodium Stearyl Fumarate, Croscarmellose sodium and Magnesium stearate.

Film-coating:

Polyvinyl alcohol, Talc, Titanium dioxide and Polyethylene glycol.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please refer outer package for expiry date.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package.

6.5 Nature and contents of container

HDPE container containing 30 & 90 tablets.

Bulk Shipment Pack.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

Aurobindo Pharma Limited,

Hyderabad, Telangana State, India.

AUROBINDO

Manufactured By

APL Healthcare Limited,
Unit-IV, Plot No.16, APIIC Multi Products SEZ,
Menakuru Village, Naidupeta Mandal,
Tirupati District,
Andhra Pradesh, INDIA

8. DATE OF PREPARATION OF THE TEXT: 15.05.2024

NDC 59651-583-30
NDC 59651-583-90
TMDA. Reg.No.: XXX XX XX XXXX
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