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Indication: Treatment of HIV-1 infection
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1 Executive Summary

1.1 Introduction: Elvitegravir (EVG, 150-mg) as a component of STRIBILD (elvitegravir, cobicistat (COBI), emtricitabine, tenofovir disoproxil fumarate), is an approved drug which has been reviewed in NDA 203-100 for the treatment of human immunodeficiency virus-1 (HIV-1). EVG belongs to a class of HIV-1 integrase strand-transfer inhibitors that prevent integration of HIV-1 genetic material into the host-cell genome. The integration of the viral genome into the host cell genome is an essential step of the HIV-1 replication cycle. Presently, Gilead Sciences has submitted a new drug application for EVG 85-mg and 150-mg tablets for the treatment of HIV-1 infection. No nonclinical pharmacology and toxicology studies were submitted: reference is made to the approved NDA 203-100.

1.2 Brief Discussion of Nonclinical Findings from NDA 203-100: The safety pharmacology, pharmacokinetics, general toxicology (single- and repeat-dose), carcinogenicity, reproductive and developmental toxicology, and special toxicology were characterized in a variety of animal models. Genotoxicity studies were conducted in in vitro and in vivo assays. Combination toxicology studies of EVG with COBI or ritonavir (increases the systemic exposures of co-administered agents) were also conducted. The rat and dog were the appropriate animal models for the toxicology studies because of the similar disposition of EVG in humans.

Elvitegravir showed modest bioavailability in rats (30% to 35%) and dogs (27% to 33%). In rats, EVG was rapidly absorbed and widely distributed. Binding to human plasma and purified human albumin was high (≥ 99.3%). Elimination from tissues paralleled that from plasma and was complete by 96 hours after dosing. EVG was extensively metabolized by oxidation, glucuronidation and combinations of the two. The most abundant metabolites were common between mouse, rat, rabbit, dog and human. The predominant metabolite was GS-9202 followed by GS-9200 and JTP-74488 (a glucuronide of GS-9202). However, the parent EVG accounted for the majority of the radioactivity in plasma.

Elvitegravir had a low potential for drug interactions through inhibition of human cytochromes P450 or P-glycoprotein. Metabolism of EVG by human hepatic microsomal fraction was reduced by CYP3A inhibitors, such as COBI and ritonavir.

In single oral dose toxicology studies in rats and dogs, no lethality was seen at dose levels of 2000 mg/kg or 1000 mg/kg, respectively. A series of GLP oral repeat-dose toxicology studies was conducted with EVG in mice (13-week), rats (4-, 13- and 26-week), and dogs (4- and 39-week). In the repeat-dose toxicology studies, two treatment-related effects included (1) the presence of lipid vacuoles in the lamina propria of the upper small intestines, and (2) changes in cecum weights and dilation of the cecum in rats and dogs.

In rats, cecal weights and/or its contents were increased at doses ≥ 300 mg/kg/day, with dilatation of the cecum observed at ≥ 1000 mg/kg/day (3-, 6-month studies). In dogs, dilatation of the cecum was observed in males at 100 mg/kg/day only in the 4-week repeat-dose study. These observations were not accompanied by any histological changes in the cecum or GI adverse events. Similar changes in the cecum have been reported with antibacterial quinolones which affect the GI microflora. Elvitegravir has a quinolone moiety and was confirmed to have
antibacterial activity in a reverse mutation assay (23.4 μg/plate) as part of the genotoxicology studies. Although the activity was much weaker than that of the antibacterial quinolones, the changes in the cecum were considered to be due to the antibacterial activity of high local concentrations of EVG in the GI tract.

Lipid-like vacuoles were observed in the lamina propria in the upper small intestine (duodenum and/or jejunum) in rats, with increased incidence and severity at doses ≥ 1000 mg/kg/day. The incidence and severity did not increase with long term dosing, and there was no evidence of toxicity or any adverse tissue reactions associated with these vacuoles. The cause of the vacuolization was considered to be related to the high local EVG concentrations to which the GI epithelium was exposed. In a series of mechanistic studies (2-week repeated oral dose toxicity study in rats with 1-, 2-, and 8-week recovery period), the vacuoles were shown to contain mainly triglycerides, and tended to disappear slowly after withdrawal of the treatment with EVG. The vacuoles formation may be related to the lipid absorption process in the GI tract, although there were no changes in plasma lipid parameters or adverse clinical observations. In dogs, lipid vacuoles containing mainly triglycerides were observed in the upper small intestinal lamina propria in both sexes at doses of 30 (mid) and 100 mg/kg/day (high) in the 39-week study. Similar to rats, these observations were also not accompanied by any GI adverse events or histological changes in the cecum or the small intestines, and they were not considered adverse. Furthermore, in the carcinogenicity study in rats, there were no notable findings in the upper small intestine, suggesting that the presence of the vacuoles was not adverse.

The NOAELs for EVG were determined to be 2000 mg/kg/day in mice and rats, and 100 mg/kg/day for dogs. The exposures based on plasma AUC values at the NOAELs in the animals were approximately 2- to 3-fold (mice), 20- to 36-fold (rats), and 2- to 3-fold (dogs) higher than the AUC in patients treated once daily with EVG150 mg.

There were no significant adverse effects observed in a 13-week combination toxicity study conducted in rats with EVG alone, COBI alone, or the combination of EVG and COBI. The combination of 1000 mg/kg/day EVG with 30 mg/kg/day COBI or with 10 mg/kg/day ritonavir (90-day study in rats) did not result in new or additive toxicity.

Elvitegravir induced a slight increase in the number of cells with chromosomal structural aberrations at levels greater than or equal to 55 μg/mL in Chinese Hamster Lung cells when tested in the 6-hour treatment without metabolic (S9) activation. However, no evidence of chromosomal aberrations was observed after 24-hour treatment without S9 up to 45 μg/mL, or in the presence of S9 up to 175 μg/mL. EVG may have a weak potential to induce chromosomal aberrations. Elvitegravir was negative for mutagenic potential in a bacterial reverse mutation test (Ames). In a micronucleus test in rats, single oral administration of EVG up to a dose of 2000 mg/kg (Cmax 43.5 μg/mL in males and 68.3 μg/mL in females) did not show any evidence of genotoxic activity for induction of chromosome damage.

Long-term carcinogenicity studies in mice (2-year) and rats (88-90 weeks) with EVG showed no carcinogenic potential at exposures 2- to 4-fold (mice) and 12- to 27-fold (rat) greater than the exposure observed in humans at the EVG 150 mg. In the mouse study, high-dose EVG (2000 mg/kg/day) was also dosed in combination with ritonavir (25 mg/kg/day). No drug-related
increases in tumor incidence were noted in these animals at exposures approximately 14-fold the human systemic exposure at the therapeutic EVG dose.

There were no EVG-related significant adverse effects observed in fertility studies in male and female. The NOAEL for reproductive parameters in the fertility studies was 2000 mg/kg/day in male and female rats at exposures approximately 16.5- to 30-fold higher than human therapeutic exposure. In embryo-fetal developmental studies in rats, there were no effects on Caesarean-sectioning, litter parameters at dose levels up to 2000 mg/kg/day. The maternal and fetal NOAEL for EVG was 2000 mg/kg/day at exposures 23-fold higher than human therapeutic exposure. In a combination study with EVG and ritonavir in rats, the maternal and fetal NOAELs were 10 mg/kg/day ritonavir and 1000 mg/kg/day EVG when administered separately or in combination at EVG exposures approximately 8-fold higher than therapeutic exposure. In rabbits, the maternal NOAEL of EVG was 50 mg/kg/day. The 150 and 450 mg/kg/day dosages were associated with reduced body weight gains and feed consumption during the post-dosage period. There were no adverse effects on embryo-fetal development and the developmental NOAEL was 450 mg/kg/day at exposures 0.2-fold higher than human therapeutic exposure.

In rats, in the perinatal/postnatal reproduction toxicity study, including the postnatal behavioral/functional evaluation, there were no adverse effects at dosages up to 2000 mg/kg/day. The maternal NOAEL for general toxicity of EVG and the NOAEL for reproduction in the dams and viability and growth in the offspring were 2000 mg/kg/day at exposures 18-fold higher than human therapeutic exposures. In the juvenile toxicity evaluation portion of the study, the only drug-related observation was increased cecum weights at 2000 mg/kg/day (high dose) for male rats and at 1000 (mid) and 2000 mg/kg/day (high) for female rats. There were no histopathological correlates for this finding in the rat. The NOAEL for toxicity of EVG was 2000 mg/kg/day for juvenile animals at exposures 7-fold higher than human therapeutic exposures.

The overall nonclinical program of EVG, including the data from the combination of COBI and EVG studies were considered adequate to support the safety of EVG 85 mg and 150 mg tablets.

1.3 Recommendations

1.3.1 Approvability: There are no nonclinical pharmacology and toxicology issues which would preclude the approval of EVG 85 mg and 150 mg tablets

1.3.2 Additional Non Clinical Recommendations: None

1.3.3 Labeling:

Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, elvitegravir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Antiretroviral Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to elvitegravir, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients by calling 1-800-258-4263.

Animal Data

Elvitegravir studies in animals have shown no evidence of teratogenicity or an effect on reproductive function. In offspring from rat and rabbit dams treated with elvitegravir during pregnancy, there were no toxicologically significant effects on developmental endpoints. The exposures (AUC) at the embryo-fetal No Observed Adverse Effects Levels (NOAELs) in rats and rabbits were respectively 23 and 0.2 times higher than the exposure in humans at the recommended daily dose of 150 mg.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies of elvitegravir were carried out in mice (104 weeks) and in rats for up to 88 weeks (males) and 90 weeks (females). No drug-related increases in tumor incidence were found in mice at doses up to 2000 mg per kg per day alone or in combination with 25 mg per kg per day ritonavir at exposures 3- and 14-fold, respectively, the human systemic exposure at the recommended daily dose of 150 mg. No drug-related increases in tumor incidence were found in rats at doses up to 2000 mg per kg per day at exposures 12- to 27-fold, respectively in male and female, the human systemic exposure.

Elvitegravir was not genotoxic in the reverse mutation bacterial test (Ames test) and the rat micronucleus assay. In an in vitro chromosomal aberration test, elvitegravir was negative with metabolic activation; however, an equivocal response was observed without activation.

Elvitegravir did not affect fertility in male and female rats at approximately 16- and 30-fold higher exposures (AUC), respectively, than in humans at the therapeutic 150 mg daily dose.

Fertility was normal in the offspring of rats exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 18-fold higher than human exposures at the recommended 150 mg daily dose.

2 Drug Information

2.1 Drug

CAS Registry Number: 697761-98-1

Generic Name: Elvitegravir

Code Name: GS-9137; JTK-303; EVG

Chemical Name: 3-Quinolinecarboxylic acid, 6-[(3-chloro-2-fluorophenyl)methyl]-1,4-dihydro-1-[(1S)-1-(hydroxymethyl)-2-methylpropyl]-7-methoxy-4-oxo-
Molecular Formula/Molecular Weight: C_{23}H_{23}ClFNO_{5}/447.88

Structure or Biochemical Description:

![Chemical Structure](image)

Pharmacologic Class: HIV-integrase inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs: IND 72,177, DMF 025187; NDA 203-100

2.3 Drug Formulation: EVG tablet is an immediate-release tablet developed in two strengths, 85 mg and 150 mg. Each tablet contains the following inactive ingredients: hydroxypropyl cellulose, sodium lauryl sulfate, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate.

2.4 Comments on Novel Excipients: None

2.5 Comments on Impurities/Degradants of Concern: Over 18 impurities and degradation products related to EVG were identified in batches of the active pharmaceutical ingredient or drug product. The multiple batches of EVG tested in the toxicology program were considered to be representative of the GMP material. The proposed specifications for impurities in the EVG drug substance were deemed acceptable based on repeat dose general toxicology studies, in silico evaluation of mutagenic potential, and the serious nature of the clinical indication. The proposed specifications for [impurity name] were also deemed acceptable based on calculated PDE values or those listed in ICH Q3C(R5). A compound specific risk assessment was made for [impurity name], a potentially genotoxic impurity. Using carcinogenicity data for this impurity, a TTC of [TTC value] μg/day was calculated. The impurities have been reviewed in NDA 203-100.

2.6 Proposed Clinical Population and Dosing Regimen: EVG will be coadministered with a ritonavir-boosted protease inhibitor and with other antiretroviral agents for the treatment of HIV-1 infection in antiretroviral treatment-experienced adults. EVG 150 mg or 85 mg tablet is administered orally, once daily, with food.

2.7 Regulatory Background: EVG as a component of STRIBILD is an approved drug which has been reviewed in NDA 203-100.
3 Studies Submitted: Gilead Sciences has referred to NDA 203-100 for the nonclinical pharmacology and toxicology studies. Those studies were reviewed as part of NDA 203-100. The following genetic toxicology has been submitted to NDA 203-093.

Mutagenicity Test of EVG Using Microorganisms

3.1 Studies Reviewed

Mutagenicity Test of EVG Using Microorganisms

3.2 Studies Not Reviewed

Exploratory studies were not reviewed.

3.3 Previous Reviews Referenced

Yes, NDA 203-100.

4. Genetic Toxicology

Mutagenicity Test of EVG Using Microorganisms

Study title:

- Study no.: K01-5135
- Study report location: EDR
- Conducting laboratory and location: [Redacted]
- Date of study initiation: March 23, 2012
- GLP compliance: Yes
- QA statement: Yes
- Drug, lot #, and % purity: RS-B-9137-2; 99.6% pure

Key Study Findings: It was concluded that EVG had no ability to induce mutations under the present test conditions. The mutagenicity of the test substance was judged to be negative.
Methods

Strains: *Salmonella typhimurium* strains TA100, TA1535, TA98 and TA1537 and *Escherichia coli* strain WP2uvrA were used.

Concentrations in definitive study: 156, 313, 625, 1250 and 5000 μg/plate

Basis of concentration selection: Dose-range study

Negative control: DMSO

Positive control: 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide, Sodium azide and 2-Aminoanthracene

Formulation/Vehicle: The test substance solution of 50.0 mg/mL prepared with DMSO

Incubation & sampling time: 37±0.5°C for 48 hours.

Results:

The number of revertant colonies in the test substance treatment groups was less than twice that in each negative control for all tester strains without and with S9 mix. The bacterial growth inhibition was observed at 625 μg/plate or more in TA100, TA1535, TA98 and TA1537 and at 5000 μg/plate in WP2uvrA without and with S9 mix. The precipitation of the test substance was observed at 2500 μg/plate or more in the absence and presence of S9 mix.

Study Validity: Yes

Study outcome: negative with or without S9.

5 Integrated Summary and Safety Evaluation

Elvitegravir is an approved drug as a component of STRIBILD (Elvitegravir 150 mg/Cobicistat 150 mg/Emtricitabine 200 mg/Tenofovir DF 300 mg Tablet) for the treatment of HIV-1 infection.

Elvitegravir demonstrated no significant effect on vital organ systems in rats and dogs in the safety pharmacology studies. In the central nervous, renal/urinary and GI systems, there were no adverse effects in rats at doses up to 2000 mg/kg. In cardiovascular and respiratory systems in conscious beagle dogs, EVG did not show any significant effects on blood pressure, heart rate, electrocardiogram, respiratory rate, or the degree of oxygen saturation at doses up to 100 mg/kg. In a hERG assay, EVG had no effect on the tail current at concentrations up to 1 μM.

Elvitegravir showed modest bioavailability in rats and dogs. In rats, EVG was rapidly absorbed and widely distributed, although it was excluded from the central nervous system and eye. Binding to human plasma and purified human albumin was high. EVG was extensively metabolized by oxidation, glucuronidation and combinations of the two. The most abundant metabolites were common between mouse, rat, rabbit, dog and human. The predominant metabolite was GS-9202 (M1), with lesser amounts of GS-9200 (M4) and M7 (JTP-74488, a glucuronide of M1). Following administration of [14C]-EVG in a human mass balance study,
94.8% of the dose was recovered in feces, consistent with the hepatobiliary excretion of EVG; 6.7% of the administered dose was recovered in urine, primarily as glucuronide metabolites, with no unchanged EVG observed. The potential for enterohepatic recirculation was low. In rats, low levels of EVG, but not its metabolites, were detectable in milk. In single- or repeat-dose nonclinical studies with EVG, no clinically-relevant target-organ toxicity was observed. However, two non-adverse findings, not considered relevant to clinical use, were observed in rats and dogs.

In rats, cecal weights and/or its contents were increased at doses ≥ 300 mg/kg/day, with dilatation of the cecum observed at ≥ 1000 mg/kg/day (3-, 6-month studies). In dogs, dilatation of the cecum was observed in males at 100 mg/kg/day only in the 4-week repeat-dose study. These observations were not accompanied by any histological changes in the cecum or GI adverse events. Similar changes in the cecum have been reported with antibacterial quinolones which affect the GI microflora. Elvitegravir has a quinolone moiety and was confirmed to have antibacterial activity in the reverse mutation assay (23.4 μg/plate). Although the activity was much weaker than that of the antibacterial quinolones, the changes in the cecum were considered to be due to the antibacterial activity of high local concentrations of EVG in the GI tract.

Lipid-like vacuoles were observed in the lamina propria in the upper small intestine (duodenum and/or jejunum) in rats, with increased incidence and severity at doses ≥ 1000 mg/kg/day. The incidence and severity did not increase with long term dosing, and there was no evidence of toxicity or any adverse tissue reactions associated with these vacuoles. The cause of the vacuolization was considered related to the high local EVG concentrations to which the GI epithelium was exposed. In a series of mechanistic studies (2-week repeated oral dose toxicity study in rats with a 1-, 2-, and 8-week recovery period), the vacuoles were shown to contain mainly triglycerides, tended to disappear slowly after withdrawal of treatment with EVG, and may be related to the lipid absorption process although there were no changes in plasma lipid parameters or adverse clinical observations. In dogs, lipid vacuoles containing mainly triglycerides were observed in the upper small intestinal lamina propria in both sexes at doses of 30 (mid) and 100 mg/kg/day (high) in the 39-week dog study. Similar to rats, these observations were also not accompanied by any GI adverse events or histological changes in the cecum and the small intestines, and they were not considered adverse. Furthermore, in the 2-year rat carcinogenicity study, there were no notable findings in the upper small intestine, further suggesting that the presence of the vacuoles was not adverse.

The NOAELs for EVG were determined to be 2000 mg/kg/day in mice and rats, and 100 mg/kg/day for dogs. The exposures based on plasma AUC values at the NOAELs in the animals were approximately 2- to 3-fold (mice), 20- to 36-fold (rats), and 2- to 3-fold (dogs) higher than the AUC in patients treated once daily with EVG at 150 mg.

Estimated safety margins (Table 1) were calculated based on exposure after repeat dosing (AUC0−t) from the 13-week mouse, 6-month rat, and 9-month dog studies with EVG, as well as exposure to EVG when administered with COBI or with ritonavir in rats. Calculations of the safety margins are based on a human AUCtau value of 23 μg•h/mL following administration of 150 mg EVG for the treatment of HIV-1 infection. While the margin of safety was approximately 2-fold in the 13-week mouse study, in the 2-year mouse carcinogenicity study.
(EVG alone or in combination with ritonavir) no adverse effects were noted at an exposure margin of approximately 14-fold. Elvitegravir exposure in the chronic toxicity studies (26-week rat and 39-week dog) exceeded the exposure at the clinical dose.

Table 1. Estimated Safety Margins for EVG 150 mg Based on Exposure (AUC) at Animal NOAELs

<table>
<thead>
<tr>
<th>Species</th>
<th>Gender</th>
<th>Study Type</th>
<th>NOAEL Dose (mg/kg/day)</th>
<th>AUC&lt;sub&gt;0-t&lt;/sub&gt; (μg h/mL)</th>
<th>Safety Margin&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>Male</td>
<td>13-week Toxicity</td>
<td>2000</td>
<td>44 - 59</td>
<td>1.9 – 2.6 X</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rat</td>
<td>Male</td>
<td>26-week Toxicity</td>
<td>2000</td>
<td>460 - 836</td>
<td>20 – 36 X</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rat + 10 mg/kg RTV</td>
<td>Male</td>
<td>13-week Combination Toxicity</td>
<td>1000</td>
<td>140 - 167</td>
<td>6.1 – 7.3 X</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rat + 30 mg/kg COBI</td>
<td>Male</td>
<td>13-week Combination Toxicity</td>
<td>1000</td>
<td>183 - 201</td>
<td>8.0 – 8.7 X</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dog</td>
<td>Male</td>
<td>39-week Toxicity</td>
<td>100</td>
<td>54 - 66</td>
<td>2.3 – 2.9 X</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

COBI, cobicistat; EVG, elvitegravir; NOAEL, no observed adverse effect level; RTV, ritonavir

<sup>a</sup> Human AUCtau 23 μg h/mL

Elvitegravir induced a slight increase in the number of cells with chromosomal structural aberrations at levels greater than or equal to 55 μg/mL in Chinese Hamster Lung cells when tested in the 6-hour treatment without metabolic (S9) activation. However, no evidence of chromosomal aberrations was observed after 24-hour treatment without S9 up to 45 μg/mL, or in the presence of S9 up to 175 μg/mL. EVG may have a weak potential to induce chromosomal aberrations. No mutagenic activity of EVG was detected in the bacterial reverse mutation test (Ames) using 4 different strains of Salmonella typhimurium and in 1 strain of Escherichia coli. The highest dose (750 μg/mL) of EVG that could be tested was limited by the growth inhibition (antibacterial) effects of EVG on the tester strains. Elvitegravir exhibited antibacterial activity at 23.4 μg/plate and above depending on the strain and test conditions. Elvitegravir did not show any significant increases in the incidence of micronucleated immature erythrocytes or any significant decreases in the proportion of immature erythrocytes. The systemic exposure to the parent drug (C<sub>max</sub>) on Day 1 was 43.5 μg/mL in males and 68.3 μg/mL in females dosed at 2000 mg/kg.

In the 2-year carcinogenicity studies, there was no increase in EVG-related tumor incidence in mice at doses up to 2000 mg/kg/day (2.4- to 3.8-fold the human systemic exposure at the therapeutic dose of 150 mg/day). Similarly in rats at doses up to 2000 mg/day/day (12- to 27-fold the human systemic exposure at the therapeutic dose), no EVG-related increase in tumor incidence was found. In the mouse study, high-dose EVG (2000 mg/kg/day) was also dosed in combination with ritonavir (25 mg/kg/day). No drug-related increases in tumor incidence were
noted in these animals at exposures approximately 14-fold the human systemic exposure at the therapeutic EVG dose.

Table 2. Estimated Safety Margins for EVG 150 mg Based on Exposure (AUC) at the High Dose in the Carcinogenicity Studies.

<table>
<thead>
<tr>
<th>Species Gender</th>
<th>Study Type</th>
<th>High Dose (mg/kg/day)</th>
<th>AUC₀₋₄ (µg*hr/ml)</th>
<th>Safety Margin*a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse Male</td>
<td>2-Year Carcinogenicity</td>
<td>2000</td>
<td>54.2</td>
<td>2.4</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>2000</td>
<td>86.6</td>
<td>3.8</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>2000</td>
<td>54.2</td>
<td>2.4</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>2000</td>
<td>86.6</td>
<td>3.8</td>
</tr>
<tr>
<td>Mouse Male</td>
<td>2-Year Carcinogenicity</td>
<td>2000+25 (ritonavir)</td>
<td>318</td>
<td>13.8</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>2000+25 (ritonavir)</td>
<td>333</td>
<td>14.5</td>
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<tr>
<td>Rat Male</td>
<td>88-90 Week Carcinogenicity</td>
<td>2000</td>
<td>285</td>
<td>12.4</td>
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<tr>
<td>Female</td>
<td></td>
<td>2000</td>
<td>617</td>
<td>26.8</td>
</tr>
</tbody>
</table>

a = Human AUCtau 23 µg•h/mL

There were no EVG-related adverse effects observed in fertility studies in male and female rats. The NOAEL for reproductive parameters in the fertility studies was 2000 mg/kg/day in rats at exposures approximately 16- to 30-fold higher than human therapeutic exposure. In the embryo-fetal development studies in rats, there were no effects on Caesarean-sectioning, litter parameters, gross external, soft tissue or skeletal fetal alterations (malformations or variations) at dose levels up to 2000 mg/kg/day. The developmental NOAEL for EVG was 2000 mg/kg/day at exposures 23-fold higher than human therapeutic exposure. In a combination embryo-fetal development study with EVG and ritonavir, the NOAELs were 10 mg/kg/day for ritonavir and 1000 mg/kg/day EVG when administered separately or in combination at exposures approximately 8-fold higher EVG than therapeutic exposure. In rabbits, the maternal NOAEL of EVG was 50 mg/kg/day (low). The 150 and 450 mg/kg/day dosages were associated with reduced body weight gains and feed consumption during the post-dosage period. There were no adverse effects on embryo-fetal development and the developmental NOAEL was 450 mg/kg/day at exposures 0.2-fold higher than human therapeutic exposure. In the developmental and perinatal/postnatal reproductive toxicology studies, including postnatal behavioral/functional and juvenile toxicity evaluation in rats, there were no adverse effects at dosages up to 2000 mg/kg/day. The maternal NOAEL for general toxicity of EVG and the NOAEL for reproduction in the dams and viability and growth in the offspring were 2000 mg/kg/day at exposures 18-fold higher than human therapeutic exposures. In the juvenile toxicity evaluation portion of the study, the drug-related observation was increased cecum weights at 2000 mg/kg/day (high) for male rats and at 1000 (mid) and 2000 mg/kg/day (high) for female rats. There were no histopathological correlates for this finding in the rat. The NOAEL for toxicity of EVG was 2000 mg/kg/day for juvenile animals at exposures 7-fold higher than human therapeutic exposures. Elvitegravir was secreted in the milk of nursing rats in the pre/postnatal study. At the 2000 mg/kg/day dose level, the EVG milk: plasma ratio was 0.1.
### Table 3. Estimated Safety Margins for EVG 150 mg Based on Exposure (AUC) at NOAELs in the Reproductive Toxicology Studies

<table>
<thead>
<tr>
<th>Reproductive Toxicology Study</th>
<th>NOAEL (mg/kg/day)</th>
<th>AUC₀⁻₄ (µg*hr/ml)</th>
<th>Safety Margin*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fertility and General Reproduction in Rat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2000</td>
<td>379</td>
<td>16.5</td>
</tr>
<tr>
<td>Female</td>
<td>2000</td>
<td>695</td>
<td>30</td>
</tr>
<tr>
<td>Embryo-Fetal Development in Rat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal</td>
<td>2000</td>
<td>535</td>
<td>23.3</td>
</tr>
<tr>
<td>Fetal</td>
<td>2000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Embryo-Fetal Development in Combination with Ritonavir in Rat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal</td>
<td>1000</td>
<td>181</td>
<td>8</td>
</tr>
<tr>
<td>Fetal</td>
<td>1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Embryo-Fetal Developmental in Rabbit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal</td>
<td>50</td>
<td>1.45</td>
<td>0.06</td>
</tr>
<tr>
<td>Fetal</td>
<td>450</td>
<td>4.27</td>
<td>0.2</td>
</tr>
<tr>
<td>Perinatal Postnatal Toxicity in Rat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal General Toxicity Reproduction in Dams</td>
<td>2000</td>
<td>408</td>
<td>18</td>
</tr>
<tr>
<td>Reproduction in Dams</td>
<td>2000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Juvenile Toxicity:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2000</td>
<td>134</td>
<td>5.8</td>
</tr>
<tr>
<td>Female</td>
<td>2000</td>
<td>194</td>
<td>8.4</td>
</tr>
</tbody>
</table>

*a = Human AUCₜau 23 µg•h/mL

Elvitegravir was neither irritating to skin or eyes, nor showed potential for phototoxicity. The immunotoxicity of EVG was evaluated in a 28-day study in rats at doses up to 1000 mg/kg/day and was not found to be immunotoxic in the rats. In a local lymph node assay in mice, EVG did not show potential to induce skin sensitization.

The most prominent metabolites of EVG were similar across rat, mice, rabbit and humans. The most prominent, GS-9200 and GS-9202 were studied in repeat dose mouse and rat studies, including the pre-/postnatal developmental toxicity and juvenile toxicity studies. Over 18 impurities and degradation products related to EVG have been identified in batches of the active pharmaceutical ingredient or drug product. Based on impurity profiles, the multiple GLP batches of EVG tested in the toxicology program were considered to be representative of the GMP material and support the specified limits of impurities proposed for commercial production.

The overall nonclinical development program with EVG has not identified any specific target organ toxicities or cause for concern.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PRITAM S VERMA
02/15/2013

HANAN N GHANTOUS
02/15/2013

I concur with the primary reviewer, that the nonclinical data support an approval action for Elvitegravir.
## PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

### NDA Number: 203-093  
Applicant: Gilead Sciences, Inc.  
Stamp Date: June 27, 2012

Drug Name: Vitekta  
NDA Type: New

On **initial** overview of the NDA application for filing:

<table>
<thead>
<tr>
<th>Content Parameter</th>
<th>Yes</th>
<th>No</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>2. Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>3. Is the pharmacology/toxicology section legible so that substantive review can begin?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>4. Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>5. If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>6. Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>7. Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>8. Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
# PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
## NDA/BLA or Supplement

<table>
<thead>
<tr>
<th>Content Parameter</th>
<th>Yes</th>
<th>No</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>9. Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m² or comparative serum/plasma levels) and in accordance with 201.57?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>10. Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>11. Has the applicant addressed any abuse potential issues in the submission?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?</td>
<td></td>
<td></td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE?**  __Yes__

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

---

Reviewing Pharmacologist  

Team Leader/Supervisor

File name: 5_Pharmaclology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908  
Reference ID: 3174635
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PRITAM S VERMA
08/15/2012

HANAN N GHANTOUS
08/15/2012