# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**21-814s005/22-292**

# PHARMACOLOGY REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

| | |
|---|---|
| NDA NUMBER: | 21-814 S005<br>21-822<br>22-292 |
| DATE RECEIVED BY CENTER: | 12/20/07 |
| PRODUCT: | APTIVUS, (tipranavir) |
| INTENDED CLINICAL POPULATION: | HIV-1 infected children |
| SPONSOR: | Boehringer Ingelheim |
| DOCUMENTS REVIEWED: | Modules 1 and 4 |
| REVIEW DIVISION: | Division of Antiviral Products |
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Date of review submission to DFS: 6/18/08

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# *EXECUTIVE SUMMARY*

## I. Recommendations

A. Recommendation on approvability

The recommendation from the pharmacology/toxicology perspective is to approve.

B. Recommendation for nonclinical studies

None.

C. Recommendations on labeling, as agreed upon with the sponsor.

**5.4 Effects on Platelet Aggregation and Coagulation**

APTIVUS/ritonavir should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other medical conditions, or who are receiving medications known to increase the risk of bleeding such as antiplatelet agents and anticoagulants, or who are taking supplemental high doses of vitamin E

In rats, tipranavir treatment induced dose-dependent changes in coagulation parameters, bleeding events and death. Co-administration with vitamin E significantly increased these effects [*see Nonclinical Toxicology (13.2)*]. However, analyses of stored plasma from adult patients treated with APTIVUS capsules and pediatric patients treated with APTIVUS oral solution (which contains a vitamin E derivative) showed no effect of APTIVUS/ritonavir on vitamin K-dependent coagulation factors (Factor II and Factor VII), Factor V, or on prothrombin or activated partial thromboplastin times .

In *in vitro* experiments, tipranavir was observed to inhibit human platelet aggregation at levels consistent with exposures observed in patients receiving APTIVUS/ritonavir.

**13.2 Animal Toxicology and/or Pharmacology**

In preclinical studies in rats, tipranavir treatment induced dose-dependent changes in coagulation parameters (increased prothrombin time, increased activated partial thromboplastin time, and a decrease in some vitamin K dependent factors). In some rats, these changes led to bleeding in multiple organs and death. The co-administration of vitamin E in the form of TPGS (d-alpha-tocopherol polyethylene glycol 1000 succinate) with tipranavir resulted in a significant increase in effects on coagulation parameters, bleeding events, and death.

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In preclinical studies of tipranavir in dogs, an effect on coagulation parameters was not seen. Co-administration of tipranavir and vitamin E has not been studied in dogs. Clinical evaluation of coagulation effects on HIV-1-infected patients demonstrated no tipranavir plus ritonavir effect and no effect of the vitamin E-containing oral solution on coagulation parameters [*see Effects on Platelet Aggregation and Coagulation (5.4)*].

## II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

At the time of the accelerated NDA 21-814 (2004) and traditional NDA 21-814 (2007) reviews, it was clear that tipranavir increased coagulation parameters (prothrombin time and activated partial thromboplastin time) in rodents but the mechanism was unknown. It was thought that this effect might be caused by an indirect mechanism related to hepatic enzyme induction in rodents. No similar changes were seen in dog studies. Monitoring of PT was performed in clinical trials and no significant changes in this parameter were observed in humans. However, intracranial hemorrhages were later seen in the clinic and, as a consequence, in 2006, the sponsor performed a series of studies to investigate the mechanism of tipranavir anti-coagulant effects in rats. The studies showed that these effects were related to levels of vitamin K-related factors [VII, IX and likely II (prothrombin)] and developed gradually over weeks. Changes did not show up in conventionally monitored coagulation parameters until factor levels decreased to a critical point. At that point, there was potential for a bleeding event. Co-administration of vitamin K prevented decreases in factors and changes in coagulation parameters. Complete recovery occurred after dosing stopped. This recovery was tied to return of normal levels of affected factors. The fact that changes in factor levels were related to vitamin K suggests an effect on the vitamin K cycle not unlike coumarin anti-coagulants, albeit more gradual. TPV also affected platelet aggregation. Arachidonic acid (AA)-induced platelet aggregation was inhibited by TPV ex vivo, was TPV dose-related and partially ameliorated by vitamin K co-administration. Inhibition of AA-induced platelet aggregation was also noted in vitro in human and rat platelet rich plasma. Vitamin E TPGS co-administered with TPV exacerbates the anti-coagulant effect of TPV. Vitamin E is known to affect vitamin K-related factors and the observed significant increase in anti-coagulant effects in the presence of vitamin E is probably due to an additive effect on vitamin K-related coagulation factors.

B. Pharmacologic activity

See accelerated NDA 21-814 review (2004).

C. Nonclinical safety issues relevant to clinical use

Major targets organs for TPV in nonclinical studies are the gastrointestinal tract and the liver [accelerated NDA 21-814 review (2004) and traditional NDA 21-814 review (2007)]. The nonclinical studies support monitoring of GI and liver function in the clinic.

Mechanistic studies on the anti-coagulant effect of tipranavir in rats suggest an effect on the vitamin K cycle not unlike coumarin anti-coagulants. The clinical relevance of this finding is not known; however, the effect is noted under Warnings and Precautions in the label.

# *2.6 PHARMACOLOGY/TOXICOLOGY REVIEW*

## 2.6.1 INTRODUCTION AND DRUG HISTORY

See traditional NDA 21-814 review (2007).

**Disclaimer**: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

**Studies reviewed within this submission:**

A 10-week oral (gavage) study in the male rat to explore the effects of tipranavir on coagulation when co-administered with Vitamin E TPGS (BI Toxicology Study No. 06R241, final report u07-3162 dated 25 May 2007).

**Studies not reviewed within this submission but reviewed within the traditional NDA 21-814 (2007)**:

Effects of tipranavir on human platelet aggregation in vitro (BI final report u06-1703 dated 2 August 2006).

22 week oral study in male rats to explore effects of tipranavir on coagulation with a 4-week recovery period (BI final report u06-3728 dated 15 December 2006).

## 2.6.2 PHARMACOLOGY

See accelerated NDA 21-814 review (2004).

### 2.6.2.1 Brief summary

### 2.6.2.2 Primary pharmacodynamics

### 2.6.2.3 Secondary pharmacodynamics

### 2.6.2.4 Safety pharmacology

**2.6.2.5 Pharmacodynamic drug interactions**

## 2.6.3 PHARMACOLOGY TABULATED SUMMARY

## 2.6.4 PHARMACOKINETICS/TOXICOKINETICS

See accelerated NDA 21-814 review (2004).

**2.6.4.1 Brief summary**

**2.6.4.2 Methods of Analysis**

[see under individual study reviews]

**2.6.4.3 Absorption**

**2.6.4.4 Distribution**

**2.6.4.5 Metabolism**

**2.6.4.6 Excretion**

**2.6.4.7 Pharmacokinetic drug interactions**

**2.6.4.8 Other Pharmacokinetic Studies**

**2.6.4.9 Discussion and Conclusions**

**2.6.4.10 Tables and figures to include comparative TK summary**

## 2.6.5 PHARMACOKINETICS TABULATED SUMMARY

[pivotal studies pertinent to the primary indication and core pharmacology studies relevant to the primary pharmacodynamic effect, as available and as provided by the sponsor]

## 2.6.6 TOXICOLOGY

See accelerated NDA 21-814 review (2004) and traditional NDA 21-814 review (2007).

**2.6.6.1 Overall toxicology summary**

Special toxicology: At the time of the accelerated NDA 21-814 (2004) review, it was clear that tipranavir increased coagulation parameters (prothrombin time and activated partial thromboplastin time) in rodents but the mechanism was unknown. It was thought that this effect

might be caused by an indirect mechanism related to hepatic enzyme induction in rodents. No similar changes were seen in dog studies. Monitoring of PT was performed in clinical trials and no significant changes in this parameter were observed in humans. However, intracranial hemorrhages were seen in the clinic and, in 2006, the sponsor performed a series of studies to investigate the mechanism of tipranavir anti-coagulant effects in rats. The studies showed that these effects were related to levels of vitamin K-related factors [VII, IX and likely II (prothrombin)] and developed gradually over weeks. Changes did not show up in conventionally monitored coagulation parameters until factor levels decreased to a critical point. At that point, there was potential for a bleeding event. Co-administration of vitamin K prevented decreases in factors and changes in coagulation parameters. Complete recovery occurred after dosing stopped. This recovery was tied to return of normal levels of affected factors. The fact that changes in factor levels were related to vitamin K suggests an effect on the vitamin K cycle not unlike coumarin anti-coagulants, albeit more gradual. TPV also affected platelet aggregation. Arachidonic acid (AA)-induced platelet aggregation was observed ex vivo, was TPV dose-related and partially ameliorated by vitamin K co-administration. Inhibition of AA-induced platelet aggregation was also noted in vitro in human and rat platelet rich plasma. Vitamin E TPGS co-administered with TPV significantly exacerbates the anti-coagulant effect of TPV. Vitamin E is known to affect vitamin K-related factors and the observed increase in anti-coagulant effects in the presence of vitamin E is probably due to an additive effect on vitamin K-related coagulation factors.

**2.6.6.2 Single-dose toxicity**

**2.6.6.3 Repeat-dose toxicity**

**2.6.6.4 Genetic toxicology**

**2.6.6.5 Carcinogenicity**

**2.6.6.6 Reproductive and developmental toxicology**

**2.6.6.7 Local tolerance**

**2.6.6.8 Special toxicology studies**

**Study title**: A 10-week oral (gavage) study in the male rat to explore the effects of tipranavir on coagulation when co-administered with Vitamin E TPGS (BI Toxicology Study No. 06R241).

**Key study findings**:

Vitamin E TPGS co-administered with TPV exacerbates the anti-coagulant effect of TPV. A previous study demonstrated the effects of TPV, administered alone, on vitamin K related factors as well as arachidonic acid-induced platelet aggregation (U06-3728). Based on literature review, vitamin E has also been shown to affect vitamin K-related factors. The increase in anti-coagulant effects is judged due to an additive effect on vitamin K-related coagulation factors.

**Study no.**: 06R241; Document number U07-3162.
**Volume #, and page #**: EDR (S005)
**Conducting laboratory and location:** Boehringer Ingelheim Pharmaceuticals, Inc., Toxicology & Safety Assessment Department, Ridgefield, CT, 06877
**Date of study initiation**: December 14, 2006
**GLP compliance**: Yes.
**QA reports**: yes (X) no ( )
**Drug, lot #, and % purity**: Tipranavir, Lot # 113011, purity 98.9 %; TPGS (D-ά-tocopherol polyethylene glycol 1000 succinate) was obtained from (b) (4).
**Formulation/vehicle**: Aqueous solution pH 10.5 for TPV (volume 15 ml/kg/day session 1) in all sessions and vitamin E TPGS in session 2 (total volume 20 ml/kg/day) and 3 (total volume 10 ml/kg/day). In session one, vitamin E TPGS vehicle was DI water (volume 20 ml/kg/day).

**Methods**

Doses:

**Dosage Regimen**

| | Session 1[a] and Session 2[b] | | Session 3[c] | |
|---|---|---|---|---|
| Group | Vit E TPGS mg/kg/day | TPV mg/kg/day | Vit E TPGS mg/kg/day | TPV mg/kg/day |
| G1 Control | 0 | 0 | 0 | 0 |
| G2 TPGS Control | 3500 | 0 | 1750 | 0 |
| G3 TPV TPGS Low | 1000 | 1200 | 500 | 600 |
| G4 TPV TPGS High | 3500 | 1200 | 1750 | 600 |
| G5 TPV | 0 | 1200 | 0 | 600 |

a Session 1: Day 1-15 (2 days of dosing, Days 1 and 2)), test articles dosed separately, 4 hours apart, at 20 ml/kg or 15 ml/kg for TPGS and TPV, respectively. Control vehicles were DI water and aqueous solution, pH 10.5.
b Session 2: Day 16 – 21 (6 days of dosing, Days 16 thru 22), test articles combined in one solution and administered at 20 ml/kg in order to reduce the total dosing volume administered to animals.
c Session 3: Day 26 – study termination (dosing all days, Days 26 thru 61, 62 or 65 giving 35, 36 or 39 days of dosing); dose levels of TPV and Vit E TPGS reduced due to overt toxicity (bleeding) and the combined dosing volume further reduced to 10 ml/kg. VK administered starting Day 47 every other day (presumably 7 or 9 days of dosing) to subgroup of animals within each dose group.

Doses:

**Dosage Regimen**

| | Session 1[a] and Session 2[b] | | Session 3[c] | |
|---|---|---|---|---|
| Group | Vit E TPGS mg/kg/day | TPV mg/kg/day | Vit E TPGS mg/kg/day | TPV mg/kg/day |
| G1 Control | 0 | 0 | 0 | 0 |
| G2 TPGS Control | 3500 | 0 | 1750 | 0 |
| G3 TPV TPGS Low | 1000 | 1200 | 500 | 600 |
| G4 TPV TPGS High | 3500 | 1200 | 1750 | 600 |
| G5 TPV | 0 | 1200 | 0 | 600 |

a Session 1: Day 1-15 (2 days of dosing, Days 1 and 2)), test articles dosed separately, 4 hours apart, at 20 ml/kg or 15 ml/kg for TPGS and TPV, respectively. Control vehicles were DI water and aqueous solution, pH 10.5.
b Session 2: Day 16 – 21 (6 days of dosing, Days 16 thru 22), test articles combined in one solution and administered at 20 ml/kg in order to reduce the total dosing volume administered to animals.
c Session 3: Day 26 – study termination (dosing all days, Days 26 thru 61, 62 or 65 giving 35, 36 or 39 days of dosing); dose levels of TPV and Vit E TPGS reduced due to overt toxicity (bleeding) and the combined dosing volume further reduced to 10 ml/kg. VK administered starting Day 47 every other day (presumably 7 or 9 days of dosing) to subgroup of animals within each dose group.

Study design: The purpose of this oral gavage study in male Sprague Dawley rats was to explore the effects of TPV on coagulation when co-administered with an excipient in TPV oral solution, Vitamin E TPGS. The study was initiated in December 2006. In the course of the study, an exacerbation of the anticoagulant effect of TPV was seen when co-administered with TPGS. A 15-day report of this finding was submitted to the FDA, covering the first 5 weeks of the 13-week study.

Male Sprague Dawley VAF+ albino rats [Crl:CD(SD)IGS BR, (b) (4) ] (30/group) were administered TPGS, TPV with or without TPGS or TPV alone. The study was run in three sessions of dosing, each session included variations in dose volume and/or dose level in order to titrate the appropriate combination tolerated by the animals. Session 1 was stopped after 2 days due to rales and death and the volume administered was lowered for the next session. Session 2 was also stopped due to high mortality. In Session 3, volumes were again reduced resulting in lower dosages of TPV and TPGS.

Morbidity and mortality checks were performed at least daily and body weights and food consumption measured weekly. Clinical signs were checked daily on days of test article administration. Coagulation parameters [prothrombin time (PT), activated partial thromboplastin time (aPTT) and fibrinogen] were measured on blood samples drawn from the jugular vein of 3 to 5 animals in Session 2 and Session 3 following 6 and 4 days of test article administration, respectively. Plasma was also sent for Thrombotest and measurement of factors II, VII, IX and X. On Day 29 (Session 3), the level of vitamin E in plasma was measured 2 hours post-dose and PTV toxicokinetics parameters were determined. Necropsies were performed on animals found dead or sacrificed moribund or at termination, liver and brain weights were measured and macroscopic observations were noted for brain, liver and any gross abnormality. Histopathology was not performed in this study.

**Results**:

**Coagulation Parameters and Factor Analysis:**

Session 2 Results:

Session 2: Summary of Coagulation Parameters after 6 days of dosing at 1200 mg/kg/day TPV (Day 22) (Percent change from G1 Control):

| Group | TPV mg/kg/day | Vit E TPGS mg/kg/day | PT | aPTT | Fibrinogen | Thrombotest |
|---|---|---|---|---|---|---|
| G1 | 0 | 0 | 14.6[a] | 18.5[a] | 246.3[a] | - |
| G2 | 0 | 3500 | 1 | 1 | -3 | 3 |
| G3 | 1200 | 1000 | 151 | 145* | 21 | 593 |
| G4 | 1200 | 3500 | 253* | 211+ | 25 | 1786* |
| G5 | 1200 | 0 | 77 | 103 | -8 | 196 |

a = means in G1 Control.
Statistical significance (mean values, not percent change): * $p \leq 0.05$, + $p \leq 0.01$.

Session 2: Summary of Changes in Factor Levels (Percent change from G1 Control) after 6 days of dosing at 1200 mg/kg/day TPV (Day 22):

| Group | TPV mg/kg/day | Vit E TPGS mg/kg/day | II | VII | IX | X |
|---|---|---|---|---|---|---|
| G2 | 0 | 3500 | -1 | -3 | -8 | -2 |
| G3 | 1200 | 1000 | -95+ | -88+ | -93+ | -54+ |
| G4 | 1200 | 3500 | -95+ | -93+ | -92+ | -55+ |
| G5 | 1200 | 0 | -83+ | -86+ | -84+ | -52+ |

Statistical significance (mean values, not percent change): * $p \leq 0.05$, + $p \leq 0.01$.

Session 2 results showed an increase in PT, aPTT and Thrombotest after administration of TPV at 1200 mg/kg/day but the increases were not statistically significant. With co-administration of TPGS, the increases were dose related to TPGS doses. Results for fibrinogen levels were very variable and not considered signifcant. Mean decreases in factor II, VII and IX levels ranged from 83% to 95%. Factor X levels were decreased by approximately 50%. These changes in Factor levels were not affected by the presence of TPGS.

Session 3 Results:

Session 3: Summary of Coagulation Parameters after 17 days of dosing (Day 43) at 600 mg/kg/day TPV (Percent change from G1 Control):

| Group | TPV mg/kg/day | Vit E TPGS mg/kg/day | PT | aPTT | Fibrinogen | Thrombotest |
|---|---|---|---|---|---|---|
| G2 | 0 | 1750 | 2 | -8 | -6 | 0 |
| G3 | 600 | 500 | 14 | 48+ | -11 | 53 |
| G4 | 600 | 1750 | 47+ | 67+ | -6 | 163+ |
| G5 | 600 | 0 | 9 | 24 | -3 | 24 |

a = means in G1 Control.
Statistical significance (mean values, not percent change): * $p \leq 0.05$, + $p \leq 0.01$.

Session 3: Summary of Changes in Factor Levels (Percent change from G1 Control) after 17 days of dosing at 1200 mg/kg/day TPV (Day 43):

| Group | TPV mg/kg/day | Vit E TPGS mg/kg/day | II | VII | IX | X |
|---|---|---|---|---|---|---|
| G2 | 0 | 3500 | 4 | 7 | 5 | 8 |
| G3 | 1200 | 1000 | -72+ | -71+ | -73+ | -41* |
| G4 | 1200 | 3500 | -72+ | -73+ | -72+ | -45+ |
| G5 | 1200 | 0 | -40+ | -50+ | -43+ | -19 |

Statistical significance (mean values, not percent change): * $p \leq 0.05$, + $p \leq 0.01$.

Session 3 results showed that following the reduction in doses of TPV and TPGS, increases in aPTT were still present in groups receiving both test articles but the magnitudes of the increases were reduced, while significant increases in PT and Thrombotest were found only in the TPV/TPGS high dose groups. There was only a trend observed in the TPV-only group. As in Session 2, increases in PT, aPTT and Thrombotest were greater when TPGS was co-administered and magnitude appeared related to TPGS dose level. No significant changes in fibrinogen were noted. Factor level decreases were of a lesser magnitude than in Session 2 but Session 3 decreases were significantly different from Control (G1) for II, VII and IX while the effect on X was variable.

Effect of Addition of VK to Subgroups in Session 3:

Session 3: Summary of Coagulation Parameters after 35 to 39 days of dosing at 600 mg/kg/day TPV plus or minus addition of VK at Day 47 to the end of the study (Percent change from G1 Control):

| Group | TPV mg/kg/day | Vit E TPGS mg/kg/day | VK | PT | aPTT | Fibrinogen | Thrombotest |
|---|---|---|---|---|---|---|---|
| G2 | 0 | 1750 | No | 2 | 1 | -4 | 2 |
| | | | Yes | 0 | -2 | 5 | -1 |
| G3 | 600 | 500 | No | 9 | 55+ | -15+ | 46+ |
| | | | Yes | 4 | -7* | -11 | 0 |
| G4 | 600 | 1750 | No | 18 | 62+ | -14* | 62* |
| | | | Yes | 9+ | -5 | -12 | 1 |
| G5 | 600 | 0 | No | 8 | 25+ | -4 | 27 |
| | | | Yes | 2 | -2 | -7 | -1 |

a = means in G1 Control.
Statistical significance (mean values, not percent change): * $p \leq 0.05$, + $p \leq 0.01$.

Session 3: Summary of Changes in Factor Levels after 35 to 39 days of dosing at 600 mg/kg/day TPV plus or minus addition of VK at Day 47 to end of the study (Percent change from G1 Control):

| Group | TPV mg/kg/day | Vit E TPGS mg/kg/day | VK | II | VII | IX | X |
|---|---|---|---|---|---|---|---|
| G2 | 0 | 1750 | No | -9 | -8 | 0 | -13 |
| | | | Yes | 1 | 1 | -1 | 1 |
| G3 | 600 | 500 | No | -68+ | -68+ | -68+ | -46+ |
| | | | Yes | 21+ | 37+ | 15* | 33* |
| G4 | 600 | 1750 | No | -71+ | -78+ | -78+ | -55+ |
| | | | Yes | 13 | 32 | -7 | 6 |
| G5 | 600 | 0 | No | -39+ | -46+ | -42+ | -35+ |
| | | | Yes | 12 | 2 | 14* | 20 |

Statistical significance (mean values, not percent change): * $p \leq 0.05$, + $p \leq 0.01$.

Session 3 VK versus no VK, at the end of the study, showed that administration of VK reversed the anti-coagulant changes observed in the absence of VK.

Fibrinogen levels were significantly decreased in TPV/TPGS groups not receiving VK but these decreases were slight and similar to those in the groups receiving VK. They are not considered related to TPV/TPGS administration.

**Mortality:**

Total mortality as of Day 30:

| Group | TPV (mg/kg/day) | TPGS (mg/kg/day) | Session | | | Total Dead |
|---|---|---|---|---|---|---|
| | | | 1 | 2 | 3 | |
| G1 | 0 | 0 | 0 | 0 | 0 | 0 |
| G2 | 0 | 3500 | 0 | 0 | | 1 |
| | 0 | 1750 | | | 1 | |
| G3 | 1200 | 1000 | 2 | 7 | | 11 |
| | 600 | 500 | | | 2 | |
| G4 | 1200 | 3500 | 0 | 15 | | 22 |
| | 600 | 1750 | | | 7 | |
| G5 | 1200 | 0 | 2 | 3 | | 5 |
| | 600 | 0 | | | 0 | |

Mortality in Session 2 was increased when TPV was administered with TPGS and the incidence increased with TPGS dose. Mortality incidence was decreased in Session 3 when dose levels of both TPV and TPGS were reduced.

Mortality was related to macroscopic observations of hemorrhage, frequently associated with gavage or bleeding techniques but thought to be primarily due to drug treatment. Hemorrhages were usually present in multiple sites including GI tract (13/36), brain (12/36), thorax (13/36), peritoneum (3/36), testis (5/36), prostate (6/36), thymus (6/36). Hemorrhage was also noted in esophagus, urinary bladder, trachea, salivary gland, lung, mesentery, eye, skeletal muscle, skin, epididymis, pancreas. The cause of death for eight animals is unknown but did not involve hemorrhage that could be detected by macroscopic observation.

**Body weight and food consumption:**

All animals receiving TPV or TPV/TPGS exhibited decreased body weight gain (8-10%) compared to Controls. Food consumption was reduced in Session 2 but returned to normal or near normal in Session 3.

**Toxicokinetics:**

TPV toxicokinetic parameters from mean concentration data on Day 29 (Session 3).

| TK parameter | Group, TPV dose (mg/kg/day) | | |
|---|---|---|---|
| | G3, 600 | G4, 600 | G5, 600 |
| $C_{max}$ (µM) | 129 | 90.4 | 99.3 |
| $AUC_{0-24}$ (µM.h) | 1,693 | 1,481 | 1,439 |
| $t_{max}$ (h) | 4 | 2 | 4 |

No differences were observed between groups receiving TPV or TPV/TPGS.

Mean plasma levels of Vitamin E on Day 29 (2 hours post-dose).

| Group | TPV (mg/kg/day) | TPGS (mg/kg/day) | Vitamin E (ng/ml) |
|---|---|---|---|
| G1 | 0 | 0 | 22.52 |
| G2 | 0 | 1750 | 47.11 |
| G3 | 600 | 500 | 37.28 |
| G4 | 600 | 1750 | 38.51 |
| G5 | 600 | 0 | 15.42 |

Vitamin E plasma levels were significantly elevated in the groups receiving 1750 mg/kg/day TPGS with or without TPV. Plasma levels were also elevated in the group receiving 500 mg/kg/day TPGS but the results were not statistically significant.

### 2.6.6.9 Discussion and Conclusions

See Overall Conclusions and Recommendations.

### 2.6.6.10 Tables and Figures 2.6.7 TOXICOLOGY TABULATED SUMMARY

**OVERALL CONCLUSIONS AND RECOMMENDATIONS**

Conclusions: The nonclinical studies submitted under the accelerated NDA 21-814 (2004) and traditional NDA 21-814 (2007) demonstrated the safety of TPV. The toxicities observed in animal studies were reversible, manageable, species specific and/or considered secondary to species-specific hepatic enzyme-including effects of tipranavir in the rodent. The nonclinical studies supported the clinical monitoring of liver and GI function.

Mechanistic studies on the anti-coagulant effect of tipranavir in rats were submitted under the traditional NDA 21-814 (2007). These studies suggest an effect on the vitamin K cycle not unlike coumarin anti-coagulants. Tipranavir also affected platelet aggregation. Studies on the effect of vitamin E TPGS co-adminisration with tipranavir were submitted under this traditional NDA 21-814 (2008). These studies demonstrate that vitamin E TPGS exacerbates the anti-coagulant effect of tipranavir. The clinical relevance of this finding is not known; however, the effect is noted under Warnings and Precautions in the label.

Recommendations: None.

Suggested labeling: See Section I. C.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

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