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**PHARMACOLOGY REVIEW(S)**

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

**PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION**

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Indication: HIV  
Applicant: Tibotec  
Review Division: DAVP  
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# 1 Executive Summary

## 1.1 Introduction

## 1.2 Brief Discussion of Nonclinical Findings

Darunavir is an HIV protease inhibitor approved for the treatment of HIV infection in various populations. Darunavir selectively inhibits the cleavage of HIV encoded Gap-Pol polyproteins in infected cells, thereby preventing the formation of mature virus particles. Darunavir is orally administered as a tablet at a concentration of 300 mg BID, 400 mg BID, or 600 mg QD with ritonavir (100 mg) and with food. The rationale for combination with a low dose of ritonavir is to improve the oral bioavailability of darunavir. Darunavir may be coadministered with other anti-retroviral agents.

Previous studies have shown the safety and effectiveness of darunavir as well as the toxicology profile. Please see the prior reviews for this drug for a complete summary of the toxicological profile.

The toxicology studies submitted with this Supplement were designed to respond to a Post-Marketing Requirement under NDA 21-976/S-6 (SDN 44) for “an embryofetal study of adequate AUC exposure in order to establish a safety profile for darunavir prior to a pregnancy protocol initiation.” The PMR was requested due to juvenile toxicology effects (CNS effects such as tremors that were related to death) as well as AUC levels for the reproductive toxicology studies that was <1. These data increased a safety concern for human trials in pregnant women that were being proposed at the time.

In the current application, three studies were submitted. Two of the studies were range finding studies in 2 species: rat and minipig with and without Ritonavir. In both species, a NOAEL was achieved in the Dams. However, in the minipig, AUC exposures did not increase significantly when boosted with Ritonavir. Therefore, the pivotal GLP toxicology study to address the PMR for reproductive toxicology was performed in the rat.

In the pivotal GLP-compliant reproductive toxicology study with Ritonavir, all dams survived to the end of dosing (except for several gavage-related mortalities). No drug-related deaths were noted. However, body weight and food consumption were decreased in dams at all doses (which did reach statistical significance). Soft and pale feces were noted at all doses (both 600 mg/kg/day and 1000 mg/kg/day of darunavir boosted with ritonavir). Due to the body weight loss and decreased food consumption at all doses, the maternal NOAEL was not determined. However, a NOAEL was achieved in the pups.

There were no changes in litter parameters (implantations, corpora lutea, resorptions, etc) at any dose. However, fetal weights were decreased in both the pups dosed during GD (gestation day) 6-11 (~5-8%) as well as the pups dosed GD 12-17 (~15-21%). The

weight changes noted at 1000 mg/kg/day was slightly more than in the 600 mg/kg day group, but the differences were not significant.

The Sponsor proposed a NOAEL in the pups to be the low dose (600 mg/kg/day darunavir + 100 mg/kg RTV). The sponsor did not give a rationale for determining that the lower dose was the NOAEL. The fetal weight losses were slightly lower in the low dose (600 mg/kg/day of darunavir), which may support this conclusion. Otherwise, findings between the low dose and the high dose groups were similar.

In the pivotal embryofetal study, an AUC for darunavir increased significantly, compared to previous embryofetal studies with darunavir. Human safety margins were calculated based on the increased AUC in rats, which ranged from 1.6 to 3.2. The range of safety margins was calculated from two dose groups (600 and 1000 mg/kg/day), two gestation day points, as well as two clinical trials. The new safety margins allowed for a significant increase over previous exposures in rats that equated to roughly 0.5x the human exposure.

Given that the submitted GLP study in rats increased the safety margins from less than 1 to ~ 3-fold and no safety signals of concern have been noted, the Sponsor has fulfilled the PMR and established an adequate safety margin for pregnant women.

### **1.3 Recommendations**

#### **1.3.1 Approvability**

The pharmacology/toxicology studies submitted to NDA 202-895 and NDA 21-976 support the labeling for this submission and are sufficient for approval.

#### **1.3.2 Additional Non Clinical Recommendations**

The Post-Marketing Requirement for NDA 21-976/S-6 (SDN 44) “an embryofetal study of adequate AUC exposure in order to establish a safety profile for darunavir prior to a pregnancy protocol initiation” has been satisfied.

#### **1.3.3 Labeling**

##### *Suggested P/T Labeling*

##### Section 8.1 Pregnancy

Pregnancy Category C: PREZISTA should be used during pregnancy only if the potential benefit justifies the potential risk.

No adequate and well-controlled studies have been conducted in pregnant women. Reproduction studies conducted with darunavir showed no embryotoxicity or teratogenicity in mice and rats in the presence or absence of ritonavir as well as in rabbits with darunavir alone. In these studies, darunavir exposures with ritonavir (based on AUC) were higher in rats (3-fold), whereas in mouse and rabbit, exposures to darunavir alone were lower (<1-fold) compared to those obtained in humans at the recommended clinical dose of darunavir boosted with ritonavir.

In the rat pre- and postnatal development study, a reduction in pup body weight gain was observed with darunavir alone or in combination with ritonavir during lactation. This was due to exposure of pups to drug substances via the milk. Sexual development, fertility and mating performance of offspring were not affected by maternal treatment with darunavir alone or in combination with ritonavir. The maximal plasma exposures achieved in rats were approximately 50% of those obtained in humans at the recommended clinical dose boosted with ritonavir.

### Section 8.4 Pediatric Use

Do not administer PREZISTA/ritonavir in pediatric patients below 3 years of age because of toxicity and mortality observed in juvenile rats dosed with darunavir. In the juvenile toxicity study where rats were directly dosed with darunavir (from 20 mg/kg to 1000 mg/kg up to days 23 to 26 of age), deaths occurred from post-natal day 5 through 11 at plasma exposure levels ranging from 0.1 to 1.0 of the human exposure levels. In a 4-week rat toxicology study, when dosing was initiated on post-natal day 23 (the human equivalent of 2 to 3 years of age), no deaths were observed with a plasma exposure (in combination with ritonavir) of 0.1 of the human plasma exposure levels. [see *Warnings and Precautions* (5.11), *Use in Specific Populations* (8.1), *Clinical Pharmacology* (12.3) and *Nonclinical Toxicology* (13.2)]

## 2 Drug Information

### 2.1 Drug

CAS Registry Number (Optional) 313682-08-5

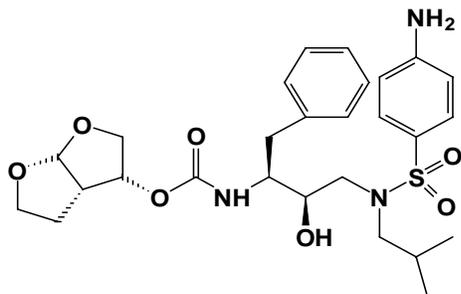
Generic Name Darunavir

Code Name TMC114

Chemical Name {3-[-amino-benzensulfonyl]-isobutyl-amino]-1-benzyl-2-hydroxy-propyl}-carbamic acidhexahydro-furo[2,3-b]furan-3-yl ester ethanolate

Molecular Formula/Molecular Weight C<sub>27</sub>H<sub>37</sub>N<sub>3</sub>O<sub>7</sub>S.C<sub>2</sub>H<sub>5</sub>OH; 593.724 (active moiety + ethanol) 547.656 (active moiety)

#### Structure or Biochemical Description



Pharmacologic Class Anti-HIV protease inhibitor

## **2.2 Relevant INDs, NDAs, BLAs and DMFs**

IND 62,477  
NDA 21-976  
NDA 202-895

## **2.3 Drug Formulation**

Tablets containing 200 mg or 400 mg darunavir base formulated as darunavir ethanolate, (b) (4) microcrystalline cellulose, (b) (4) and magnesium stearate

## **2.4 Comments on Novel Excipients**

None

## **2.5 Comments on Impurities/Degradants of Concern**

None

## **2.6 Proposed Clinical Population and Dosing Regimen**

HIV infected patients

## **2.7 Regulatory Background**

The FDA review team requested a Post Marketing Requirement for an embryofetal study of adequate AUC exposure in order to establish a safety profile for darunavir prior to a pregnancy protocol initiation. Prior embryofetal studies had exposure values below 1, which significantly affected the risk assessment for a pregnancy protocol.

# **3 Studies Submitted**

## **3.1 Studies Reviewed**

Pilot Rat DART study  
Rat DART study  
Pilot Minipig DART study

## **3.2 Studies Not Reviewed**

All studies were reviewed.

## **3.3 Previous Reviews Referenced**

None.

## 9 Reproductive and Developmental Toxicology

### 9.2 Embryonic and Fetal Development

**Study title:** Pilot oral developmental toxicity study of TMC114 in the rat.

Study no.:	TMC114-TiDP3-NC397
Study report location:	EDR
Conducting laboratory and location:	Janssen R & D Beerse Site Belgium
Date of study initiation:	March 24, 2009
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	TMC114, batch ZR319064EIA201, 99.1% pure

#### Key Study Findings

The overall goal of the study was to compare 2 doses of darunavir (1000 and 2000 mg/kg/day) without boosting with RTV to a dose of darunavir 1000 mg/kg with RTV boosting.

There were marked effects on body weight performance with darunavir at the dose level of 2000 mg/kg/day. Fetal effects (resorptions and a higher post-implantation loss and a decrease in live fetuses) were noted at the 2000 mg/kg/day level. No major effects were noted at 1000 mg/kg/day of darunavir (with or without RTV).

Furthermore, there was a substantial increase in pharmacokinetics of darunavir with RTV boosting. Therefore, with the favorable PK at 1000 mg/kg (with RTV), the fetal affects at 2000 mg/kg (without RTV), and the lack of effects at 1000 mg/kg (with RTV) the dose of 1000 mg/kg darunavir + RTV boosting was considered acceptable for the definitive study based on acceptable PK and toxicity profiles.

#### Methods

Doses:	See table below
Frequency of dosing:	See dosing days in table below
Route of administration:	Oral administration (to dams)
Dose volume:	See below
Formulation/Vehicle:	60% or 100% PEG 400 for TMC 114 and 40% PEG 400 for RTV
Species/Strain:	Female Sprague Dawley rats (CRL)
Number/Sex/Group:	See table below
Age:	9-10 weeks
Weight:	164 to 275 grams
Satellite groups:	None.
Unique study design:	None.
Deviation from study protocol:	No significant deviations.

Code	Group (colour code)	Female Nos.	Dose level		Concentration mg eq/mL	Dosing days of pregnancy	Volume mL/kg/dose
			mg eq/kg/dose	mg eq/kg/day			
V	Vehicle (blue)	1 - 8	0	0	0	6 - 17	5
L	Low A (red)	21 - 26	500	1000	100	6 - 11	5
	Low B (red bar)	27 - 32	500	1000	100	12 - 17	5
H	High A (yellow)	41 - 46	1000	2000	200	6 - 11	5
	High B (yellow bar)	47 - 52	1000	2000	200	12 - 17	5
SH	S High A (green)	61 - 66	500+RTV	1000+RTV	100 + 40	6 - 11	5 + 1.25
	S High B (green bar)	67 - 72	500+RTV	1000+RTV	100 + 40	12 - 17	5 + 1.25

### Observations and Results

For simplicity, the Sponsor referred to the groups as *Low (A) and Low (B), High (A) and High (B), and Super High (A) and Super High (B)*. See table above. The A and B designations were made to separate GD 6-11 (A group) from GD 12-17 (B group).

- Low (A): 1000 mg/kg/day Darunavir (TMC114) for GD 6-11.
- Low (B): 1000 mg/kg/day Darunavir for GD 12-17
- High (A): 2000 mg/kg/day Darunavir for GD 6-11.
- High (B): 2000 mg/kg/day Darunavir for GD 12-17.
- Super High (A): 1000 mg/kg/day Darunavir + 100 mg/kg RTV for GD 6-11.
- Super High (B): 1000 mg/kg/day Darunavir + 100 mg/kg RTV for GD 12-17

### Toxicokinetics

The addition of Ritonavir substantially increased the darunavir AUC and Cmax on day 11 (from 284 ug-h/ml to 419 ug-h/ml) and day 17 (275 ug-h/ml to 397 ug-h/ml) in both GD groups compared to Darunavir alone. (See table below.)

**Pharmacokinetics of Darunavir with or without RTV boosting in Rats**

Subset	A (D6→D11 of pregnancy)			B (D12→D17 of pregnancy)		
Group	Low A	High A	SuperHigh A	Low B	High B	SuperHigh B
Dose TMC114 (mg eq./kg/day)	2 x 500 <sup>1)</sup>	2 x 1000 <sup>1)</sup>	2 x 500 <sup>1)</sup>	2 x 500 <sup>1)</sup>	2 x 1000 <sup>1)</sup>	2 x 500 <sup>1)</sup>
Dose Ritonavir (mg/kg/day)	-	-	2 x 50 <sup>1)</sup>	-	-	2 x 50 <sup>1)</sup>
	<b>Day 6 of pregnancy First day of dosing</b>			<b>Day 12 of pregnancy First day of dosing</b>		
C <sub>max1</sub> (ng/ml)	11510	11430	9453	12547	11547	10690
C <sub>max2</sub> (ng/ml)	22633	26433	15500	24867	15017	23800
T <sub>max1</sub> – T <sub>max2</sub> (h)	1 - 7	2 - 8	6 - 7	2 - 7	1 - 8	1 - 7
AUC <sub>0-24 h</sub> (ng.h/ml)	227922	291125	284023	222196	197548	275134
AUC <sub>0-inf</sub> (ng.h/ml)	277746	332406	NR <sup>2)</sup>	248211	226923	NR <sup>2)</sup>
	<b>Day 11 of pregnancy 6 days of dosing</b>			<b>Day 17 of pregnancy 6 days of dosing</b>		
C <sub>max1</sub> (ng/ml)	8510	5813	24000	7910	5413	20000
C <sub>max2</sub> (ng/ml)	9643	7683	22233	8660	7177	30833
T <sub>max1</sub> – T <sub>max2</sub> (h)	1 - 7	6 - 7	2 - 7	1 - 7	6 - 7	1 - 7
AUC <sub>0-24 h</sub> (ng.h/ml)	104373	107401	418581	96669	103223	396979

<sup>1)</sup> *Bid* (*bis in die* = twice a day) dosing; 6 hours apart.

<sup>2)</sup> NR: not reported since AUC<sub>0-inf</sub> values were calculated with > 25% extrapolation.

**Study title:** Oral Developmental Toxicity Study of TMC114 in the Rat.

Study no.: TMC114-TiDP3-NC398  
Study report location: EDR  
Conducting laboratory and location: Janssen R & D  
Beerse Site  
Belgium  
Date of study initiation: May 18, 2010  
GLP compliance: Yes  
QA statement: Yes  
Drug, lot #, and % purity: TMC114, batch 09P0202, 99.6% pure

**Key Study Findings**

All dams survived to end of dosing (except for several gavage-related mortalities). No drug-related deaths noted. However, body weight and food consumption were decreased in dams at all doses (which did reach statistical significance). Soft and pale feces was noted at all doses.

Maternal NOAEL: Not determined due to body weight loss and decreased food consumption at all doses.

There were no changes in litter parameters (implantations, corpora lutea, resorptions, etc) at any dose. However, fetal weights were decreased both the pups dosed during GD (gestation day) 6-11 (~5-8%) as well as the pups dosed GD 12-17 (~15-21%). The weight changes noted at 1000 mg/kg/day was slightly more than in the 600 mg/kg day group, but the differences were not significant.

Fetal NOAEL: Determined to be the low dose (600 mg/kg/day TMC114 + 100 mg/kg RTV). The sponsor did not give a rationale for determining that the lower dose was the NOAEL. The fetal weight losses were slightly lower in the low dose (600 mg/kg/day), which may support this conclusion. Otherwise, findings between the low dose and the high dose groups were similar.

The Sponsor, however, did achieve an increased pharmacokinetic AUC compared to previous studies in rats. The PK of the rats was roughly 2.1x the human exposure (2.61 ug-h/ml for rat vs 124 ug-/ml for human). This was a significant increase over previous AUCs in rats that equated to roughly 0.5x the human exposure.

**Methods**

Doses: See table below  
Frequency of dosing: See dosing days in table below  
Route of administration: Oral administration (to dams)  
Dose volume: See below  
Formulation/Vehicle: 60% or 100% PEG 400 for TMC 114 and 40% PEG 400 for RTV  
Species/Strain: Female Sprague Dawley rats (CRL)

Number/Sex/Group: See table below.  
 Age: 63-70 days  
 Weight: 205-285 g  
 Satellite groups: See table below.  
 Unique study design: None.  
 Deviation from study protocol: No significant deviations.

Code	Group (colour code)	Female numbers		Dose level (TMC114/RTV)		Concentration mg eq/mL (TMC114/RTV)	Dosing days of pregnancy	Volume mL/kg/dose
		Main	TK	mg eq/kg/dose	mg eq/kg/day			
V	Vehicle (blue)	1 - 24	25 - 30	0	0	0	6 - 17	5/1.25
L	Low A (red)	41 - 64	65 - 70	300/50	600/100	60/40	6 - 11	5/1.25
	Low B (red bar)	71 - 94	95 - 100				12 - 17	5/1.25
H	High A (Green)	111 - 134	135 - 140	500/50	1000/100	100/40	6 - 11	5/1.25
	High B (Green bar)	141 - 164	165 - 170				12 - 17	5/1.25

## Observations and Results

For simplicity, the groups are referred to as *Low (A) and Low (B)* as well as *High (A) and High (B)*. See table above. The A and B designations were made to separate GD 6-11 (A group) from GD 12-17 (B group).

- Low (A): 600 mg/kg/day TMC114 + 100 mg/kg RTV for GD 6-11.
- Low (B): 600 mg/kg/day TMC114 + 100 mg/kg RTV for GD 12-17
- High (A): 1000 mg/kg/day TMC114 + 100 mg/kg RTV for GD 6-11.
- High (B): 1000 mg/kg/day TMC114 + 100 mg/kg RTV for GD 12-17.

## Maternal Results:

### Mortality

Maternal mortality was monitored 1x daily. 4 females died on study (1 Low B, 1 High B, and 2 High A). The deaths were attributed to gavage error.

### Clinical Signs

Maternal signs were monitored 1x daily. Pale feces in all groups. Reduced feces in High (B). Some of the High (A) females had increased piloerection and audible respiration which appeared to be dose related. The findings in the High (A) females was not statistically significant.

### Body Weights

Measured days 0, 4, 6-12, 14, 18, 21. Body weight loss was noted in all groups on GD 6-11 (but recovered) and GD 12-17 (did not recover).

### Feed Consumption

Maternal feed was measured days 0, 6, 10, 12, 14, 18, 21. Food consumption decreased with body weight decreases.

### Gross Pathology

Maternal pathology was evaluated at sacrifice. No changes were noted. Pathology on the females that were sacrificed prematurely revealed trauma consistent with accidental dosing.

### Litter Data:

#### Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

- Pregnancy parameters (corpora lutea, implantations, resorptions, live/dead fetuses, implantation loss) were not affected at any dose. There was a slight increase in litter loss in some High (A) dose females (1000 mg/kg/day, days 6-11) due to poor maternal condition (maternal toxicity) rather than direct effects on the embryo.

#### Offspring (Malformations, Variations, etc.)

Fetal weight loss significantly increased at GD 12-17 in both males and females at both doses (see below). The loss was dose dependent with a decrease of ~21% at the 1000 mg/kg/day dose and ~16% at the 600 mg/kg/day dose.

#### Fetal weight loss (males)

Dose of DRV	Body weight change – gms (% body wt loss)	
	GD 6-11	GD 12-17
Control (vehicle)	5.81	
600 mg/kg/day	5.49 (5%)	4.91 (15%)
1000 mg/kg/day	5.41 (7%)	4.57 (21%)

Fetal weight loss (females)

Dose of DRV	Body weight change – gms (% body wt loss)	
	GD 6-11	GD 12-17
Control (vehicle)	5.55	
600 mg/kg/day	5.13 (8%)	4.65 (16%)
1000 mg/kg/day	5.08 (8%)	4.38 (21%)

Sex ratio was normal. No major external or visceral changes. Increased incidence of incompletely descended thymus in GD 6-11 animals. This indicated a slight developmental delay (commonly observed in low weight animals).

**Toxicokinetics**

TK parameters of TMC114 was comparable for both group A and group B (referring to GD days 6-11 and 12-17). After the first day and 6 days of dosing, AUC values increased somewhat less than dose-proportionally to rather dose proportionally over the studied dose levels in Subset A/B.  $C_{max}$  and AUC values were comparable in Subset A/B for each group.

Generally,  $C_{max1}$  values (the first  $C_{max}$ ) were comparable to higher,  $C_{max2}$  values (the second  $C_{max}$ ) were comparable to lower,  $AUC_{0-6h}$  values were comparable to higher and  $AUC_{0-24h}$  values were comparable to lower after 6 days of dosing compared to the first day of dosing in Subset A and B.

## Pharmacokinetics of Darunavir (TMC114)

Sex Subset Dosage group Dose Ritonavir (mg/kg/day) Dose TMC114 (mg eq./kg/day)	Females			
	A		B	
	L	H	L	H
	<b>100</b>	<b>100</b>	<b>100</b>	<b>100</b>
	<b>600</b>	<b>1000</b>	<b>600</b>	<b>1000</b>
Day	<i>Day 6_1<sup>st</sup> day of dosing</i>		<i>DAY 12_1<sup>st</sup> day of dosing</i>	
C <sub>max1</sub> (ng/ml)	9817	12077	9687	13560
C <sub>max2</sub> (ng/ml)	21867	34533	20067	23567
T <sub>max1</sub> (h)	1	2	2	1
T <sub>max2</sub> (h)	8	7	7	8
AUC <sub>0-6 h</sub> (ng.h/ml)	46597	57974	47791	53416
AUC <sub>0-24 h</sub> (ng.h/ml)	280021	423436		
Day	<i>Day 11_6 days of dosing</i>		<i>Day 17_6 days of dosing</i>	
C <sub>max1</sub> (ng/ml)	11300	12850	17357	12933
C <sub>max2</sub> (ng/ml)	14033	23150	14200	24100
T <sub>max1</sub> (h)	6	2	1	2
T <sub>max2</sub> (h)	7	7	8	7
AUC <sub>0-6 h</sub> (ng.h/ml)	55847	69417	75318	49210
AUC <sub>0-24 h</sub> (ng.h/ml)	202282	283190	261244	218748

C<sub>max1</sub>, C<sub>max2</sub>: peak plasma concentrations after 1<sup>st</sup> and 2<sup>nd</sup> daily ritonavir/TMC114 dose (both expressed after 1<sup>st</sup> daily ritonavir/TMC114 dose)

T<sub>max1</sub>, T<sub>max2</sub>: time at peak plasma concentrations after 1<sup>st</sup> and 2<sup>nd</sup> daily ritonavir/TMC114 dose (both expressed after 1<sup>st</sup> daily ritonavir/TMC114 dose)

## Pharmacokinetics of Ritonavir

Sex Subset Dosage group Dose Ritonavir (mg/kg/day) Dose TMC114 (mg eq./kg/day)	Females			
	A		B	
	L	H	L	H
	<b>100</b>	<b>100</b>	<b>100</b>	<b>100</b>
	<b>600</b>	<b>1000</b>	<b>600</b>	<b>1000</b>
Day	<i>DAY 6_1<sup>st</sup> day of dosing</i>		<i>DAY 12_1<sup>st</sup> day of dosing</i>	
C <sub>max1</sub> (ng/ml)	2130	748	1543	704
C <sub>max2</sub> (ng/ml)	3497	3327	2173	1116
T <sub>max1</sub> (h)	2	2	1	2
T <sub>max2</sub> (h)	8	7	8	7
AUC <sub>0-6 h</sub> (ng.h/ml)	8609	3571	4765	3034
AUC <sub>0-24 h</sub> (ng.h/ml)	34863	33769		
Day	<i>Day 11_6 days of dosing</i>		<i>Day 17_6 days of dosing</i>	
C <sub>max1</sub> (ng/ml)	346	430	1640	439
C <sub>max2</sub> (ng/ml)	733	326	1132	1128
T <sub>max1</sub> (h)	1	2	1	1
T <sub>max2</sub> (h)	7	7	8	7
AUC <sub>0-6 h</sub> (ng.h/ml)	1338	1270	6280	1216
AUC <sub>0-24 h</sub> (ng.h/ml)	4041	3888	18250	5547

C<sub>max1</sub>, C<sub>max2</sub>: peak plasma concentrations after 1<sup>st</sup> and 2<sup>nd</sup> daily ritonavir/TMC114 dose (both expressed after 1<sup>st</sup> daily ritonavir/TMC114 dose)

T<sub>max1</sub>, T<sub>max2</sub>: time at peak plasma concentrations after 1<sup>st</sup> and 2<sup>nd</sup> daily ritonavir/TMC114 dose (both expressed after 1<sup>st</sup> daily ritonavir/TMC114 dose)

## Dosing Solution Analysis

Dosing solutions were made from stock solutions. QC on these solutions was acceptable.

**Study title:** Combined PK/DRF Study in Female Minipigs

Study no.: TMC114-TiDP2-NC399 TOX9288  
 Study report location: EDR  
 Conducting laboratory and location: (b) (4)  
 Date of study initiation: Feb 25, 2009  
 GLP compliance: No  
 QA statement: No  
 Drug, lot #, and % purity: TMC114, batch ZR319064EIA201, 99.4% pure

**Key Study Findings**

TMC114 was not well tolerated by the minipig. Adverse clinical signs were noted in all groups. The single dose (Phase 1 -- a BID dosing scheme, 6 hrs apart) resulted in most animals in all groups vomiting on one or both dosing occasions. Several animals were noted to be less active/passive or even subdued. During the Phase 2 repeat-dose BID scheme (9 hrs apart), vomiting, passivity, and soft/watery feces was noted. Although improved tolerance was noted with time, the dose was considered to be unacceptable for future embryofetal toxicity testing in minipigs.

In Phase 2 B (repeat dose QD), the clinical conditions were better throughout the day, although passiveness and soft feces were noted in all groups 1 hour after dosing. The signs were considered acceptable for repeated testing. Therefore, a QD testing scheme appeared to result in acceptable toxicity in minipigs with tolerable adverse events.

**Methods**

Doses: 500 or 1000 BID (Phase 1)  
 250 or 500 BID or 250 BID with RTV (Phase 2)  
 See tables below  
 Frequency of dosing: See tables below  
 Route of administration: Oral administration (to dams)  
 Dose volume: See below  
 Formulation/Vehicle: PEG 400  
 Species/Strain: Göttingen SPF minipigs from (b) (4)  
 Number/Sex/Group: 9 pigs total (3 groups of 3 pigs -- see tables below)  
 Age: 7-8 months old  
 Weight: 15-18 kg  
 Satellite groups: See table below.  
 Unique study design: None.  
 Deviation from study protocol: No significant deviations.

**Phase 1: One day dose phase**

The groups, dose levels, animal numbers and colour codes were as follows:

Group	Day of dosing	Dose* (TMC114)	Total daily dose* (TMC114)	Dose concentration* (TMC114)	Animal Nos	Colour code
		(mg eq/kg - BID)	(mg/kg - BID)	(mg eq/ml)	Female	
1	1	500	1000	100	1 - 3	White
2	1	1000	2000	200	4 - 6	Blue
3	1	500 + Ritonavir	1000	100	7 - 9	Green

\* A conversion factor of 1.08 was used at the preparation.

BID = Twice daily, 6 hours apart

**Phase 2a: Repeat dose phase**

The groups, dose levels, animal numbers and colour codes were as follows:

Group	Day of dosing	Dose* (TMC114)	Total daily dose* (TMC114)	Dose concentration* (TMC114)	Animal Nos	Colour code
		(mg eq/kg - BID)	(mg eq/kg - BID)	(mg eq/ml)	Female	
1	29-34	250	500	50	1 - 3	White
2	29-34	500	1000	100	4 - 6	Blue
3	29-34	250 + Ritonavir	500	50	7 - 9	Green

\* A conversion factor of 1.08 was used during preparation.

BID = Twice daily

**Phase 2b: Repeat dose phase**

Group	Day of dosing	Dose* (TMC114)	Total daily dose* (TMC114)	Dose concentration* (TMC114)	Animal Nos	Colour code
		(mg eq/kg)	(mg eq/kg)	(mg eq/ml)	Female	
1	35-41	250	250	50	1 - 3	White
2	35-41	500	500	100	4 - 6	Blue
3	35-41	250 + Ritonavir	250	50	7 - 9	Green

\* A conversion factor of 1.08 was used during preparation.

**Observations and Results**

This study was performed in order to evaluate the Minipig as a possible model for DART studies with TMC114. Tolerance and TK were the major endpoints.

TMC114 was evaluated with or without RTV boosting by oral gavage to minipigs for a single day or at lower repeated doses.

## Toxicokinetics

Surprisingly, RTV boosting did not result in significant increases in TMC114 levels in minipigs. Although there was a slight increase in TMC114 AUC levels, it was not significant, compared to TMC114 alone.

	First day of dosing				Last day of dosing	
	C <sub>max</sub> <sub>1</sub> ng/ml	C <sub>max</sub> <sub>2</sub> ng/ml	AUC <sub>0-24h</sub> ng.h/ml	AUC <sub>0-48h</sub> ng.h/ml	C <sub>max</sub> <sub>1</sub> ng/ml	AUC <sub>0-24h</sub> ng.h/ml
<b>Phase 1 (Day 1): bid dosing (6 hours of interval)</b>						
<b>Group 1:</b> 2 x 500 mg eq./kg TMC114	6947	12067	189630	344192	-	-
<b>Group 2:</b> 2 x 1000 mg eq./kg TMC114	9647	14840	238017	358445	-	-
<b>Group 3:</b> 2 x 500 mg eq./kg TMC114 + 2 x 50 mg/kg Ritonavir	7227	11360	180939	344792	-	-
<b>Phase 2a (Day 29-&gt;34): bid dosing (9 hours of interval)</b>						
<b>Group 1:</b> 2 x 250 mg eq./kg/day TMC114	3650	7977	109457	-	-	-
<b>Group 2:</b> 2 x 500 mg eq./kg/day TMC114	3863	14047	159422	-	-	-
<b>Group 3:</b> 2 x 250 mg eq./kg/day TMC114 + 2 x 50 mg/kg/day Ritonavir	4383	8720	114848	-	-	-
<b>Phase 2b (Day 35-&gt;41): qd dosing</b>						
<b>Group 1:</b> 250 mg eq./kg/day TMC114	-	-	-	-	6017	59299
<b>Group 2:</b> 500 mg eq./kg/day TMC114	-	-	-	-	8067	81535
<b>Group 3:</b> 250 mg eq./kg/day TMC114 + 50 mg/kg/day Ritonavir	-	-	-	-	5640	71484

Note: Minipigs (6 out of 9) vomited after the second dose occasion on Day 1 and Day 29.

No minipigs vomited on Day 41.

## 11 Integrated Summary and Safety Evaluation

Darunavir (Prezista®) is an HIV protease inhibitor approved for the treatment of HIV infection in various populations.

The toxicology studies submitted with this Supplement to fulfill a post marketing requirement “an embryofetal study of adequate AUC exposure”. These studies were performed in order to establish a safety profile for darunavir to support a pregnancy protocol that was proposed at the time of the PMR. The nonclinical studies were requested after safety concerns were mounted due to juvenile toxicology effects in rats (CNS effects such as tremors that were related to death). Due to these toxicities, combined with a low margin of safety (from AUC exposure margin in mice, rats, and rabbits from previous developmental toxicity studies that were <1), the review team issued the PMR for an embryofetal study that would increase the safety margins for pregnant women.

Three studies were submitted in the current application. Two studies were pilot studies in the rat and the minipig (with and without Ritonavir). In both the rat and minipig, a NOAEL was achieved. The rat, unlike the minipig, exhibited a significant increase in AUC after ritonavir boosting. Therefore, the rat was used for the pivotal GLP toxicology study to address the PMR.

In the pivotal reproductive toxicology study, all of the rat dams survived to the end of dosing (except for several gavage-related mortalities). The toxicities in the rat dams were limited to body weight decreases, food consumption decreases, soft feces, and pale feces at all doses (both 600 mg/kg/day and 1000 mg/kg/day of darunavir boosted with ritonavir). Due to the body weight and food consumption decreases, there was no NOAEL for the rat dams.

In the pups, there were no changes in litter parameters (implantations, corpora lutea, resorptions, etc) at any dose. Similar to the dams, fetal weights decreased at all time points and doses. The weight decreases at 1000 mg/kg/day was slightly (but not significantly) more than in the 600 mg/kg day pups.

Although there were body weight decreases at both the low dose (600 mg/kg/day) and the high dose (1000 mg/kg/day), the lack of significant body weight decreases or any other toxicities at 600 mg/kg allowed a NOAEL estimation at 600 mg/kg/day.

The PK for darunavir in the rats did increase with ritonavir boosting. The overall increase in safety margins based on the new PK data from rats ranged from 1.6 to 3.2 (see table below). The safety margin ranges varied based on calculations using: exposure in the animals (600 mg/kg or 1000 mg/kg) or exposure values from different gestation days (GD) in rats, as well as the AUC values from clinical trials in naïve or treatment experienced adults. This increase of ~3-fold increased the overall safety margin in humans from the prior safety factor of ~0.5-fold.

**Table 1: NOAEL and Safety Margins for Darunavir in Pregnant Rats**

Toxicity	Species	NOAEL (mg/kg) M/F	Safety Margin Based on AUC for naïve adults*	Safety margin based on AUC for treatment experienced adults**
Body weight loss and fetal weight loss	Rat (dam)	Not determined	---	
	Rat (pup)	600 mg/kg (M/F) GD 11 or GD 17	2.3 or 3.0	1.6 or 2.1
		1000 mg/kg (M/F) GD 11 or GD 17	3.2 or 2.5	2.3 or 1.8

\*AUC in naïve adults: 88 µg.hr/ml at 600 mg/day boosted with RTV.

\*\* AUC in treatment experienced adults: 123 µg.hr/ml at 600 mg/day boosted with RTV.

With the increase in the safety margins from the rat AUC (from less than 1 to ~ 3-fold), combined with the lack of any concerning safety signals, the Sponsor has established an adequate safety margin for pregnant women.

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/s/  
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LAINÉ P MYERS  
08/31/2011

HANAN N GHANTOUS  
08/31/2011

## PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA Number: 202-895**

**Applicant: Tibotec**

**Stamp Date: 3/29/2011**

*Cross reference NDA 21-976*

**Drug Name: Darunavir**

**NDA Type: Supplement with  
Post-Marketing P/T Studies**

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

	Content Parameter	Yes	No	Comment
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?	x		Three studies are included which were in response to a PMR from NDA 21-976.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	x		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	x		
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)?	x		
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).	x		
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 <u>submitted</u> a rationale to justify the alternative route?	x		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	x		

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA\_BLA or Supplement  
010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA/BLA or Supplement**

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x		
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?		x	No modifications to Section 8.1 were proposed to reflect the new Embryofetal development study in rats. Paragraph 2 of section 8.1 should be updated.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			N/A
11	Has the applicant addressed any abuse potential issues in the submission?			N/A
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

**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.

The Sponsor should update the label in section 8.1 to reflect the new Embryofetal Development data in rats which was submitted to fulfill a PMR.

Laine Peyton Myers, PhD April 28, 2011  
 \_\_\_\_\_  
 Reviewing Pharmacologist Date

Hanan Ghantous, PhD, DABT April 28, 2011  
 \_\_\_\_\_  
 Team Leader/Supervisor Date

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA\_BLA or Supplement  
010908

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/s/  
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LAINÉ P MYERS  
05/25/2011

HANAN N GHANTOUS  
05/26/2011