アイセントレス錠600mg
に関する資料

MSD 株式会社

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1 OVERVIEW OF THE NONCLINICAL TESTING STRATEGY

Within this application, the Applicant is not submitting any additional nonclinical data as the Applicant has not conducted any new nonclinical studies for raltegravir to support approval in the patient population. The raltegravir 1200 mg Once Daily (QD) development program and application are fully supported by nonclinical studies previously conducted in support of the raltegravir 400 mg twice daily (BID) regimen (ISENTRESS®). For supporting nonclinical data for raltegravir, the Applicant refers to ISENTRESS® NDA 22-145 and the EU MA for ISENTRESS® EMEA/H/C/000860. Based on the absence of any new nonclinical data or additional information not provided in this nonclinical overview, no 2.6 modules (pharmacology, pharmacokinetics, toxicology) for raltegravir 1200 mg QD will be submitted.

Raltegravir (also known as ISENTRESS®, MK-0518 and [redacted]) is an integrase strand transfer inhibitor that is active against HIV-1. Raltegravir for once daily use (a 1200 mg dose consisting of two 600 mg tablets) allows for a simplified dosing regimen that will provide a convenient backbone for antiretroviral therapy regimens and will allow flexibility in the choice of other additional once daily agents that could improve patient compliance and satisfaction.

2 PHARMACOLOGY

No new nonclinical pharmacodynamic studies have been conducted to support the raltegravir 1200 mg QD development program. Findings from in vitro studies previously conducted in support of raltegravir 400 mg BID regimen pertain to raltegravir 1200 mg QD as they are independent of the formulation or frequency of its administration. These studies included: comprehensive evaluation of its in vitro biochemical and antiviral activities including its resistance profile, its activity against other enzymes and receptors, and its antiviral activity in combination with other antiretroviral agents. The safety pharmacology studies previously conducted in support of the raltegravir 400 mg BID application demonstrated that raltegravir evoked no significant ancillary pharmacological or behavioral effects when evaluated on a diverse range of physiological functions (cardiovascular, neurobehavior, respiratory) in vivo.

3 PHARMACOKINETICS

No new nonclinical pharmacokinetic studies have been conducted to support the raltegravir 1200 mg QD development program. The nonclinical pharmacokinetic studies previously conducted in support of raltegravir 400 mg BID regimen included: comprehensive evaluation of absorption, distribution, metabolism, and excretion (ADME) of raltegravir in rats and dogs (two species selected for the toxicological evaluation of the compound); the metabolism in CD-1 mice, the second species in which the carcinogenic potential of raltegravir was studied; evaluation of raltegravir as a substrate, inhibitor and inducer of major cytochrome P450 (CYP) and UDP-glucuronosyltransferases (UGT) enzymes. For the purpose of interspecies comparisons between nonclinical animal models and humans, protein binding, metabolism, and excretion of raltegravir in humans were also discussed. In addition, the assessment of the inhibitory effect of raltegravir on major human drug uptake and efflux transporters was presented in the publication by the Applicant [Ref. 4.3: 03Z7Q3]. The findings from the above studies conducted in support of raltegravir 400 mg BID regimen, including the in vitro

assessment of raltegravir drug-drug interaction (DDI) potential, are applicable to raltegravir 1200 mg QD.

Key in vitro human data presented in previous regulatory submissions and the publication by Applicant [Ref. 4.3: 03Z7Q3] that are used for assessment of raltegravir 1200 mg QD DDI potential are summarized below.

Raltegravir is not a substrate of CYP enzymes and therefore, it is not expected to be a victim of DDIs via CYP inhibition or induction. Raltegravir is eliminated mainly by metabolism via a UGT1A1-mediated glucuronidation pathway and therefore, co-administration of potent UGT1A1 inhibitors or inducers may alter plasma levels of raltegravir.

In vitro, raltegravir does not inhibit (IC_{50}>100 µM) CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A, or induce CYP1A2, CYP2B6 and CYP3A4. In addition, raltegravir is not a potent inhibitor (IC_{50}>50 µM) of the UGTs tested (UGT1A1, UGT2B7) or the major human drug efflux and uptake transporters in vitro. Raltegravir does not inhibit P-glycoprotein and inhibits only 22% of breast cancer resistance protein (BCRP)-mediated transport at 100 µM. Raltegravir does not inhibit organic anion transporting polypeptide (OATP) 1B1, and it shows 40% inhibition of OATP1B3 and 16% inhibition of organic cation transporter (OCT)1 at 100 µM in vitro. In vitro, raltegravir also does not inhibit OCT2 and is not a potent inhibitor of organic anion transporter (OAT)1 and OAT3 (IC_{50} of 108 µM and 18.8 µM, respectively), and multidrug and toxin extrusion proteins (MATE)1 and MATE2-K (52% and 29% inhibition at 100 µM, respectively) [Ref. 4.3: 03Z7Q3].

Based on in vitro data, raltegravir has overall, a low propensity to perpetrate clinically meaningful DDIs with substrates of major drug metabolizing enzymes or drug transporters at plasma concentrations following 1200 mg QD administration (median C_{max} of 16.8 µM; calculated unbound C_{max} of 2.8 µM). The potential for raltegravir to inhibit the renal uptake transporter OAT3 at maximal concentrations following 1200 mg QD cannot be completely excluded based on in vitro data, however clinically meaningful DDI via this mechanism is unlikely [**Sec. 2.7.2.3.3.1**]. Additional details on the DDI profile for raltegravir 1200 mg QD can be found in [**Sec. 2.7.2.3.3.1**].

4 TOXICOLOGY

No new nonclinical toxicity studies have been conducted to support the raltegravir 1200 mg QD development program. The nonclinical toxicity studies previously conducted in support of raltegravir 400 mg BID regimen support clinical administration of raltegravir 1200 mg QD. All excipients in the raltegravir 1200 mg QD tablet are commonly used in pharmaceutical manufacturing, and no new impurities or degradation products were identified in the drug product.

The previously conducted toxicology program for raltegravir consisted of in vitro and in vivo studies for genotoxicity, acute oral toxicity and toxicokinetic studies in mice, rats and dogs, subchronic and chronic studies of up to 14 week duration in mice, up to 27 week duration in rats and up to 53 week duration in dogs, developmental and reproductive toxicity studies in

rats and rabbits and oral carcinogenicity studies in rats and mice. Doses tested in safety assessment studies were based upon demonstration of maximum tolerated and/or maximum feasible doses or demonstration of plateau of exposure. All pivotal studies were conducted in compliance with Good Laboratory Practice Regulations (GLPs) and consistent with the International Committee for Harmonization (ICH) Guidelines. All pivotal studies were supported by toxicokinetic measurements either within the study or from studies conducted under the same conditions and utilizing identical doses administered in the same vehicle.

Differences in the plasma exposures in humans administered a raltegravir 1200 mg QD dose when compared to raltegravir 400 mg BID dose have been determined in clinical evaluation; presentation of the systemic exposure multiples in pivotal toxicity and reproductive toxicity studies to the raltegravir 1200 mg QD dose are provided in [Table 2.4: 1]. In the previous application supporting the raltegravir 400 mg BID clinical dose, safety margins were based on an $AUC_{0\text{-}24}$ exposure of 54.28 µM•hr and Cmax of 7.38 µM (approximate Cmax [$C_{0.25h}$]) determined when 400 mg raltegravir BID was dosed in combination with 300 mg q.d. atazanavir and 100 mg q.d. ritonavir in healthy subjects. For raltegravir 1200 mg QD, the median $AUC_{0\text{-}24hr}$ was 54.6 µM•hr and median C_{max} was 16.8 µM. Because co-dosing with atazanavir is not recommended with raltegravir 1200 mg QD, see **[Sec. 2.7.2]**, no additional pharmacokinetic factor was determined to account for potential raltegravir exposure changes with raltegravir 1200 mg QD co-administration with atazanavir (as was done for the raltegravir 400 mg BID program).

Table 2.4: 1 Expected Human Systemic Exposures with Raltegravir Tablet Formulations

	400 mg BID[a]	**1200 mg QD[b]**
$AUC_{0\text{-}24hr}$ (µM•hr)	54.28	54.6
Cmax (µM)	7.38	16.8

[a] Therapeutic exposure identified in initial application for ISENTRESS® [NDA 22-145 and EU MA EMEA/H/C/000860]. Reflects 400 mg raltegravir BID dosed in combination with 300 mg q.d. atazanavir and 100 mg q.d. ritonavir in healthy subjects
[b] Therapeutic exposure based on mean exposures results from Protocol 292 **[Sec. 2.7.2]**

The following table [Table 2.4: 2] compares raltegravir systemic exposures in pivotal toxicity and reproductive toxicity studies relative to both raltegravir 1200 mg QD and raltegravir 400 mg BID formulations.

Table 2.4: 2: Raltegravir Systemic Exposure Multiples in Pivotal Toxicity and Reproductive Toxicity Studies

Species	Study[a]	NOAEL Dose Levels (mg/kg/day)	Animal Systemic Exposures at NOAEL		Exposure Multiples to raltegravir 400 mg BID dose[bc]		**Exposure Multiples to raltegravir 1200 mg QD dose[bd]**	
			AUC_{0-24hr} (µM hr)	Cmax (µM)	AUC_{0-24hr} (µM hr)	Cmax (µM)	**AUC_{0-24hr} (µM.hr)**	**Cmax (µM)**
Mouse[b]	3 Month Toxicity Study	50	14.5[f]	9.4[f]	<1X	2X	**<1X**	**<1X**
Rat[b]	6 Month Toxicity Study	120	57.5	18.8	1.5X	4X	**1.5X**	**1.5X**
Dog[b]	Intravenous 7-Day Toxicity Study	30	195	96.1	6X	23X	**6X**	**10X**
Dog[b]	9/12[e] Month Toxicity Study	360	273	87.4	8.5X	21X	**8.5X**	**9X**
Rat[b]	Male & Female Fertility	600	178[f]	64.3[f]	5X	13.5X	**5X**	**6X**
Rat[b]	Combined Embryo-Fetal Developmental and Pre- and Postnatal Toxicity Study	300 (embryofetal development) 600 (pre and postnatal development)	120[f] 155[f]	38.2[f] 42.5[f]	3.4X 4.3X	8X 9X	**3.4X** **4.3X**	**3.5X** **4X**
Rabbit	Embryo-Fetal Developmental Toxicity Study	1000	201[f]	37.4[f]	3.7X	5X	**3.7X**	**2X**
Rat[b]	Juvenile Toxicity Study	600	67	38.5	2X	8X	**2X**	**3.5X**
Mouse[b]	Two Year Carcinogenicity Study	250 (males) and 400 (females)[g]	36.2[f] (males) 55.5[f] (females)	22.4[f] (males) 28.8[f] (females)	1X 1.5X	5X 6.5X	**1X** **1.5X**	**2X** **3X**
Rat[b]	Two Year Carcinogenicity Study	300 (males) and 600 (females)[g]	35.8[f] (males) 294[f] (females)	10.4[f] (males) 143[f] (females)	1X 8.5X	2X 30X	**1X** **8.5X**	**1X** **13.5X**

NOAEL= no-observed-adverse-effect level; BID = twice-daily; QD = once daily

[a] Oral studies unless otherwise indicated.

[b] Exposure multiples (safety margins) adjusted for differences in plasma proteins across species. Raltegravir showed a modest binding to plasma proteins in the species studied (rats, mice, dogs and humans); rabbit plasma protein binding was not evaluated. Values for the unbound fraction in plasma were 26%, 30%, 30%, and 17% for rats, mice, dogs and humans, respectively. All calculated exposure multiples, with the exception of AUC exposure multiples from rat and rabbit embryofetal development toxicity studies, are generally presented as rounded to the nearest 0.5X or 1X.

[c] For a 400 mg BID market approved raltegravir dose in combination with 300 mg q.d. atazanavir and 100 mg q.d. ritonavir in healthy humans, median raltegravir AUC_{0-24hr} exposures of up to 54.28 µM hr may be attained.

[d] A 1200 mg QD dose (consisting of administration of two 600 mg reformulated raltegravir tablets) in Protocol 292 resulted in a AUC_{0-24hr} of 54.6 µM•hr and median C_{max} of 16.8 µM. [Sec. 2.7.2]

[e] At the NOAEL dose animals were treated at a dose level of 5 mg/kg/day for 14 weeks. Commencing at the start of week 15 and continuing until the end of the study, animals assigned to this dose group were treated at 360 mg/kg/day.

[f] Exposure data was not collected on the specific study. Exposure data were obtained from similar or shorter duration repeat dose toxicity or toxicokinetic studies where the same dose was used in the applicable species.

[g] NOAEL doses in the carcinogenicity studies were the highest doses tested (reflect maximum tolerated chronic oral dose).

The previously conducted nonclinical toxicity evaluation demonstrated that raltegravir is generally well-tolerated. Maximum oral and intravenous doses based on tolerability, formulation feasibility and/or plateau of exposure were used in toxicity studies to define the toxicity profile of raltegravir, with safety margins for the 1200 mg raltegravir dose determined for each of the toxicities identified. Effects in rodents (mortality, body weight loss, and non-glandular stomach irritation) were attributed to the nonclinical raltegravir formulation's well-characterized bulk dosing volume and local irritant effect following oral gavage of the nonclinical formulation and are not considered of significant risk to humans. There were no adverse effects in dogs up to the highest doses tested (plateau in systemic exposure).

In developmental and reproductive toxicity studies, raltegravir has been shown not to pose a hazard to reproduction or to the developing fetus based on studies in rats and rabbits. In developmental toxicity studies in rats, a slight increase in the incidence of supernumerary ribs relative to control was found at the top dose of 600 mg/kg/day. There were no external or visceral abnormalities and no other fetal or postnatal developmental effects at this dose. The safety margin at the no-observed-effect level (NOEL) for developmental toxicity in rats is approximately 3.4-fold relative to the expected human AUC in patients administered therapeutic doses of raltegravir (either raltegravir 1200 mg QD or raltegravir 400 mg BID); in rabbits, no developmental toxicity was found at the maximum dose of 1000 mg/kg/day, resulting in a safety margin of about 3.7-fold relative to the expected maximal human AUC at the therapeutic dose. In a toxicokinetic study in pregnant and lactating rats, raltegravir was shown to cross the placental barrier with fetal exposure values up to 1.5- to 2.5-fold greater than in maternal plasma drug concentrations and was also present in rat milk at concentrations about 3-fold compared to plasma. There were no effects on male or female fertility, on prenatal and postnatal development or on juvenile development in rats orally administered raltegravir.

Raltegravir was not genotoxic in a battery of in vitro assays in bacteria and mammalian cells designed to detect mutagenicity, direct DNA damage, or clastogenicity. Raltegravir was not shown to be a direct carcinogen when administered to rats and mice for 2 years. Localization of raltegravir to the nose/nasopharynx was determined to occur from routine techniques of oral gavage with periodic aspiration of dosing material into the nose and nasopharynx, resulting in secondary neoplastic findings attributed to chronic irritation and inflammation present within the nasopharynx and nose. The irritation potential of raltegravir was previously demonstrated in shorter duration rodent studies and in local tolerance studies. Based on the proposed mechanism, the observed neoplasia of the nose and nasopharynx of rats is considered to have minimal relevance to humans.

5 INTEGRATED OVERVIEW

Within this application, the Applicant is not submitting any additional nonclinical data as the Applicant has not conducted any new nonclinical studies for raltegravir to support approval in the patient population. The raltegravir 1200 mg once-daily (QD) development program is fully supported by nonclinical studies previously conducted for the raltegravir 400 mg twice daily (BID) regimen (ISENTRESS®). For supporting nonclinical data for raltegravir, the Applicant refers to ISENTRESS® NDA 22-145 and the EU MA for ISENTRESS®

EMEA/H/C/000860. Based on the absence of any new nonclinical data or additional information not provided in this nonclinical overview, no 2.6 modules (pharmacology, pharmacokinetics, toxicology) for raltegravir 1200 mg QD will be submitted [**Appendix 1**].

The nonclinical pharmacodynamics, pharmacokinetic and toxicity studies conducted to support administration of raltegravir 400 mg BID support raltegravir 1200 mg QD. The systemic exposures (daily AUC) used to calculate exposure margins for 400 mg raltegravir BID and 1200 mg raltegravir QD are equivalent (approximately 54 µM.hr) based on recommended raltegravir therapeutic use. With respect to C_{max} exposures, the raltegravir 400 mg BID dose C_{max} was identified as 7.38 µM, while for raltegravir 1200 mg QD, the median C_{max} was 16.8 µM. The exposure value used for BID dosing accounts for the clinically observed increase in raltegravir exposure when co-dosed with atazanavir; the AUC exposure value used for QD dosing reflects raltegravir not influenced by concomitant atazanavir administration, as co-dosing of raltegravir 1200 mg QD with atazanavir is not recommended, see [**Sec. 2.7.2**]. Presentation of the systemic exposure multiples in pivotal toxicity and reproductive toxicity studies to the raltegravir 1200 mg QD dose is provided in this nonclinical overview for raltegravir 1200 mg QD, with safety margins determined. Nonclinical evaluation with raltegravir has not demonstrated any direct potential toxicity relevant to human risk. The nonclinical data previously conducted for raltegravir 400 mg BID (ISENTRESS®) support the application of the raltegravir 1200 mg QD formulation.

6 LIST OF REFERENCES

[Ref. 4.3: 03Z7Q3] Rizk ML, Houle R, Chan GH, Hafey M, Rhee EG, Chu X. Raltegravir has a low propensity to cause clinical drug interactions through inhibition of major drug transporters: an in vitro evaluation. Antimicrob Agents Chemother. 2014 Mar;58(3):1294-301.

Appendix 1 Justification for Omission of Module 2.6 and 4.2 Sections

Raltegravir 1200 mg QD: Justification for Omission of Module 2.6 and 4.2 Sections		
Module	**Section Name**	**Justification for Omission**
2.6.1	Nonclinical Introduction	Not applicable, as the 2.6 modules are not included with this application. Information relevant to this application is included in Module 2.4 (Nonclinical Overview).
2.6.2, 2.6.3	Pharmacology Written and Tabulated Summaries	No new nonclinical pharmacodynamic or pharmacology studies have been conducted to support the raltegravir 1200 mg QD development program. Findings from in vitro studies previously conducted in support of raltegravir 400 mg BID regimen pertain to raltegravir 1200 mg QD as they are independent of the formulation or frequency of its administration.
2.6.4, 2.6.5	Pharmacokinetic Written and Tabulated Summaries	No new nonclinical pharmacokinetic studies have been conducted to support the raltegravir 1200 mg QD development program. The nonclinical pharmacokinetic studies previously conducted in support of raltegravir 400 mg BID regimen are applicable to raltegravir 1200 mg QD.
2.6.6, 2.6.7	Toxicology Written and Tabulated Summaries	No new nonclinical toxicity studies have been conducted to support the raltegravir 1200 mg QD development program. The nonclinical toxicity studies previously conducted in support of raltegravir 400 mg BID regimen support raltegravir 1200 mg QD use. All excipients in the raltegravir 1200 mg QD tablet are commonly used in pharmaceutical manufacturing, and no new impurities or degradation products were identified in the drug product.
4.2	Nonclinical Study Reports	No new pharmacology, pharmacokinetic or toxicology studies have been conducted to support the raltegravir 1200 mg QD development program. The raltegravir 1200 mg QD development program is fully supported by nonclinical studies previously conducted for the approved raltegravir 400 mg BID regimen.