CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020859

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

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NDA 20-859
Sonata™ (Zaleplon, 5 & 10 mg Tablet)

Type of submission: NME
Submission Date: December 30, 1997, July 31, 1998

Sponsor: Wyeth Ayerst

Indication: Insomnia

REVIEWER: Rae Yuan, Ph.D

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Biopharmaceutics Section

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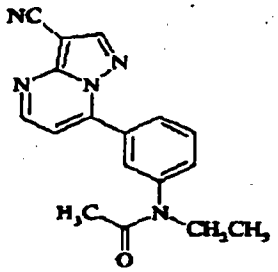
SYNOPSIS

Zaleplon has been developed as a non-benzodiazepine hypnotic agent, which has a chemical name N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethylacetamide (MW=305, its structural formula is shown below.). Its partition coefficient in octanol/water is a constant (log P= 1.23). It is a weak base with pH (range of 1-9) independent solubility of 0.2 mg/ml.



ZALEPLON

Pharmacology studies demonstrated that zaleplon binds selectively to the brain omega-1 receptor situated on the alpha subunit of the $GABA_A$ receptor complex. Pharmacokinetic studies showed that it is rapidly absorbed and rapidly eliminated in humans. The proposed administration of the drug is 10 mg p.o. dose qd before sleep. The combination of the pharmacokinetic and pharmacological features of zaleplon results in its overall beneficiary pharmacodynamic profile as having rapid onset, low degree of acute memory impairment and psychomotor function impairment, little sedative residual effect, and no daytime anxiety effect.

The reviewer took a new approach in reviewing this NDA. Instead of following the tradition review sequence on studies submitted by the sponsor, the reviewer evolved her review based on a series of questions being addressed at different stages of a drug development. The examples of some questions are listed in the box inserts in the following text.

CLINICAL PHARMACOLODY

Pharmacokinetics (PK):

-How was the first dose in human derived ?
-What are the basic PK parameters and what do they suggest about the drug ?
-Are there any active/toxic metabolite, do they accumulate ?
-How variable is the drug, where is the source of variation ?

The first dose of zaleplon in human was based on a body-weight normalized dose derived from the animal effective/toxic study. According to the sponsor, 1 mg dose was initially projected in human by taking no more than 1/600 of LD_{50} in rat (LD_{50}=500 mg /kg). An initial 5 mg was also calculated by taking no more than 1/60 of the maximum tolerated dose in s.c. rat study. The highest dose in human was proposed to be 90 mg, 1/67 of LD_{50} in dogs (100 mg/kg). In addition, in animals only 1/3 of the amount of zaleplon was needed to produce similar behavioral effects as a known hypnotic agent flurazepam does. Assuming that zaleplon was 100% available in human, the projected dose was 5-20 mg. These extrapolations, in this reviewer's opinion, are arbitrary. The animals have different metabolic profile and PK characteristics of zaleplon compared to that in human.

After single dosing of zaleplon from 1 mg to 60 mg, AUC and Cmax of the drug are linear with respect to the dose. The t1/2 and Tmax (both 1 hr) are not significantly different among the different doses. Therefore, pharmacokinetics of the drug is dose-independent. However, the clinical evaluation shows significant dose-dependent and time-dependent side-effects of the drug. More CNS side effects are noticed at 60 mg than other dosing levels, especially at 2.5 hr after dosing. This implies a possible counter-clock hysterisis of CNS effects at high dosing levels. After multiple dosing of 15 or 30 mg zaleplon for 10 days, AUC and t1/2 of the drug are similar on day 1 and day 10, indicating no accumulation of the drug. However, in 30 mg group, Tmax on day 10 is prolonged by 2 hr and Cmax is decreased to 33 ng/ml from 60 ng/ml on day 1. The constant value of AUC on day 1 and day 10 indicates that the extent of the bioavailability of the drug, which is most likely decided by the metabolism of the drug, is not altered. Instead, the absorption of the drug is likely reduced.

Absorption— Zaleplon is well absorbed and highly metabolized. Approximately 88% of the total administered radiolabeled drug and its metabolites are recovered in urine (71%) and feces (17%), where < 0.1% is the unchanged drug. The absolute bioavailability of the drug is 30%, thus, presystemic extraction ratio is 70% (E=1-F). This indicates that zaleplon PK is prone to be affected by other drugs that alter the bioavailability of zaleplon by affecting the metabolism of zaleplon. Taking the drug with food delays the Tmax from 1.4 to 3.7 hr, and decreases Cmax from 23 to 15 ng/ml after 10 mg oral administration, possibly by affecting the GI transitient time. But food does not affect the total exposure to the drug (AUC=60 ng.hr/ml). After oral dosing, zaleplon exhibits 50%-60% inter-subject variability in AUC and Cmax, compared with 20-30% variability after iv dosing, indicating that half of the PK variation of the drug comes from the absorption or presystemic metabolism process. Intra-subject variability has not been assessed.

Distribution —Zaleplon is well distributed to the tissue with Vss being 90L after IV dosing. Protein binding of the parent drug is approximately 60%, of the desethyl metabolite is 77%, and both are concentration independent. This indicates little likelihood of the transient effect of zaleplon interfering with highly protein bound drugs. From 10-55ng/ml blood concentration, zaleplon partitions from blood to plasma at a constant ratio of 1.1.

Metabolism — Zaleplon (ZAL), Desethyl-ZAL (DZAL), 5-oxo-DZAL (M1) and 5-oxo-ZAL (M2) have been identified *in vivo* and *in vitro* in human plasma and excretes. *In vivo*, the major species in plasma are parent drug (7.2%), M2 and its glucuronide (68%), and M1 (2.4%). DZAL accounts for <1% of the total drug in blood circulation. No parent drug appears in the excretes, and M2 and M2 glucuronide are the major metabolites found in urine (22 and 35% respectively). Unidentified metabolites account for 4% of the total dose in urine, but they are undetectable in plasma. *In vitro*, human liver produces different metabolic profile compared to the animal models. In humans, the major metabolite M2 is formed by aldehyde oxidase (AO) in cytosol, which also catalyzes M1 formation from DZAL but at a slower rate. CYP3A4 catalyzes DZAL formation from ZAL, and it may also be responsible for M1 formation from M2 at a much lower rate. The relative catalytic activity of AO and CYP3A4 can not be determined, because the in vitro studies determining these two enzyme activities have used supra-therapeutic substrate concentrations (50 uM-2.5 mM) in two isolated cellular fraction systems. A large variation exist in both AO (50 fold difference) and CYP3A (30 fold difference) activity in ZAL metabolism, which may contribute to the 50% variability found in Cmax and AUC.

Elimination — The elimination half-life of the parent drug is 1 hr, after either IV or oral dosing, indicating that the elimination of zaleplon is independent of the route of administration. The mass balance study shows that half-life of total radioactivity in plasma is 3.2 hr, and in blood is 1.6 hr, indicating that no metabolite with especially long half-life exists in the blood.

PK and PD Relationship:

-Is PK related to PD of the drug ?
-How is the relationship derived ?
-Does the relationship help to justify the dosing regimen in Phase 2 and 3 ?

Ideally, pharmacokinetics (PK) of a drug should be used as a surrogate marker for its pharmacodynamics (PD). This requires PK to be derived directly from the same patient population. In the case of zaleplon, no PK study has been performed in insomnia patients. It is assumed that PK in healthy volunteers are the same as in insomnia patients. PD measurements include psychomoter test battery, observer or self-rated sedation test, and EEG recording, which reflect the adverse effect of the drug (according to the medical officer). Two double-blind studies had been conducted in 10 healthy volunteers to establish PK-PD relationship. In one study, concentrations of zaleplon at 10 and 20 mg showed some relationship with pharmacodynamic effect and no hysteresis was observed. However, because of the limited range of plasma concentration, the maximum effect of

the drug could not be obtained. At best, a polynomial model was fitted to the observed plot of concentration vs. effect. Interesting to note, a counter-clock hysteresis of the side-effect at 20 mg zaleplon but not at 10mg was observed in the other study, where no statistical significant difference between 10 and 20 mg of zaleplon was noticed on all 12 psychophysical tests. All effects tested were significantly different from placebo at 1 hr and returned to baseline by 4-5 hr after dosing, indicating no significant residual effect of the drug. The reason for different observation on PK-PD relationship between the two studies is still under the pursuit, but could be due to the different washout time (2 days vs. 2-7 days) and/or different investigators. In an attempt to establish a model to describe the PK/PD relationship, the sponsor fitted a set of fixed PK parameters, obtained from all phase I studies, to the dynamic measurements obtained from 6 subjects with drug addiction history. An indirect model was the best model obtained, which provided IC_{50} of the drug as 295 ng/ml. However, two factors make it inappropriate to apply this model to the patients experiencing insomnia. First, the PK information used in the modeling was not derived from the same subject providing PD information. Secondly, the subjects in the study have drug addiction history which could result in different PD response from the patients with no drug abuse history. A further analysis on the PK-PD relationship of zaleplon is currently being pursued by the OCPB review team.

Special Populations:

-Based on the above info, what are the special populations need to be studied ?
-What are the changes in the special populations ? PK or PD ?
-How is the PK/PD knowledge applied to the dosing in special population ?

The established knowledge on PK, PD and PK-PD relationship should help to individualize drug dosing. Special populations that exhibit altered PK or PD usually require dose adjustment, the magnitude of which should, at best, be determined by the estimated PK-PD relationship.

Age and gender — No significant pharmacokinetic difference has been observed among young men, young women, elderly men and elderly women who took 5 or 10 mg zaleplon, although a statistically insignificant trend in clearance is noted with the rank order of young women > elderly (men=women) > young men. A population PK modeling of the drug, which has not been performed by the sponsor, may help to confirm the influence (or absence of influence) of age and gender on PK of zaleplon.

Race — Pharmacokinetics and safety of zaleplon examined in 5 Japanese healthy subjects demonstrate that Cmax and AUC of zaleplon increase proportionally with dose from 1-40 mg, with the exception of a slight disproportionality at 20 mg. Cross-study comparison shows that at a given dose, drug exposure of zaleplon in Japanese population is ~70% higher than in North American or European populations. This difference has not been explored by the sponsor, but can not be explained by the body weight, as attempted by this reviewer. A population PK modeling of the drug, which has not been performed by the sponsor, would helpful to confirm the influence of ethnicity on PK of zaleplon. Once

the lower clearance of zaleplon in Asian population is confirmed, dose adjustment in this group may be needed.

Zaleplon in nursing milk — Zaleplon is detected in the breast milk, where the drug has similar t1/2 and Tmax as in plasma. Milk concentrations are 50% of the plasma concentrations at all time points, until undetectable at 6 hr after dosing. Assuming the volume of excreted milk being 100 ml, the sponsor points out that the amount of zaleplon recovered in milk accounts for only 0.013% to 0.017% of the maternal dose. Assuming a 3 hr feeding schedule, the accumulative amount at 3-6 hr accounts for 0.003% to 0.006% of the drug. The sponsor states that zaleplon in milk is not a major safety concern. However, the reviewer takes a conservative approach and assumes that the volume of distribution of zaleplon in a newborn is 0.5 L/kg (adopted from other low protein bound drugs, such as ampicillin, cefotaxime, and gentamicin), and bioavailability in baby is 100%. She estimates that the concentration of the newborn will be ~12 ng/ml in 4 kg newborn. This concentration is similar to 30 ng/ml in 70 kg adult after 10 mg dosing. Considering that the safety profile and pharmacokinetic characteristics of this drug are unknown in the newborns, this drug should not be given to the nursing women.

Hepatic Impairment — As expected for a drug which is eliminated predominantly by hepatic metabolism, zaleplon PK is markedly affected by liver disease. In subjects with severe liver disease (Child Pugh Index >7), the Cmax and AUC of the drug increase 3 times and 7 times of the respective value in healthy subjects. . In subjects with moderate liver disease (Child Pugh Index <7), the respective increase are 2 and 4 fold. Elimination half-life increases significantly from 1.0 hr in healthy subjects to 2-3 hr in liver diseased subjects. Tmax in the severely diseased group delays from the value in healthy subjects, but not to a statistically significant extent. DZAL, which is normally undetectable in healthy subjects, is measurable in the liver diseased subjects until 3-4 hr after dosing. Its Cmax and AUC_{0-t} increase with the severity of liver disease. Unconjugated free M2 metabolite, on the other hand, is lower in Cmax and AUC_{0-t} in the liver diseased subjects than in the healthy subjects. Interesting to note, total M2 concentration including free M2 and its glucuronide conjugates, has a 46% higher AUC in the severely diseased subjects than in the healthy subject or moderate diseased subjects. Due to the high levels of drug in the severe liver diseased group, zaleplon should not be used in these patients. Dose adjusted to half of the recommended dose should be used in patients with mild and moderate liver disease.

Renal Impairment —As expected for a highly metabolized drug, pharmacokinetics of zaleplon do not change with impaired renal functions. However, free M2 and M2 glucuronide in dialysis patients accumulate, respectively, to 3.4 times and 11 times of the value in healthy subjects. Though apparent M2-induced adverse effects have not been reported, special attention to the toxicity of the drug should be given to patients with marked accumulation of this molecule.

Drug Interactions:

-Based on PK of NME, what types of drug interaction are expected ?
-Is the interacting drug a good choice for the interaction ?
-Based on PK/PD, is the interaction leading to dose adjustment ?

Because of PK characteristics of zaleplon, drugs affecting zaleplon metabolism are most likely to cause alteration of its kinetics. No in vitro drug interaction study on how zaleplon affects other drugs metabolism has been performed.

Zaleplon with Rifampicin — Rifampicin is a strong CYP3A4 inducer. Multiple dosing of rifampicin (600 mg qd for 13 days) reduces both Cmax and AUC of zaleplon to 25% of its respective value, caused by a 5 fold increase in zaleplon oral clearance. The possible maximum increase in systemic clearance of zaleplon is 50% (from 60 L/hr to 90 L/hr, ie, the hepatic blood flow). The observed increase in zaleplon oral clearance indicates that rifampicin increases zaleplon intrinsic clearance and thereby enhances its pre-systemic clearance. Rifampicin does not affect Tmax of zaleplon and reduces zaleplon t1/2 by 20%. The PK of free M2 is not affected by rifampicin, but Cmax and AUC_{0-t} values of free M1 are increased to 2 fold. However, the glucuronide conjugates of these two metabolites under rifampicin treatment have not been studied. The sponsor has not studied the effect of rifampicin on DZAL concentration, either. Since DZAL formation is catalyzed by CYP3A4, its level is likely to be induced by rifampicin treatment. Because of the difficulty in quantitatively assessing the induction effect on zaleplon metabolism by different rifampicin dose, patients who are on rifampicin treatment and need hypnotic agent should be given an alternative non-CYP substrate drug.

Zaleplon with Cimetidine — Cimetidine is known to inhibit CYP3A4 and AO. Single dosing of 800 mg cimetidine increases zaleplon Cmax and AUC by 85% each. This corresponds to 44% decrease in zaleplon oral clearance and 20% increase in half-life. Tmax of zaleplon is not significantly affected by cimetidine. Cmax and AUC of M2 following cimetidine treatment are 15% lower than the respective values when zaleplon is administered alone. Because zaleplon is a highly extracted drug, a small reduction in extraction can produce marked increase in systemic bioavailability, which is determined by hepatic metabolism rather than absorption (since it is a highly absorbed drug). The reduction of cimetidine in M2 level indicates that cimetidine inhibits AO-based zaleplon metabolism. Zaleplon adjusted to half of the proposed dose in patients taking cimetidine is recommended.

Zaleplon with Imipramine — Imipramine exerts some sedative hypnotic side effects. Single dosing of 75 mg imipramine does not affects the PK of 20 mg zaleplon (single dose), and vice versa. However, additive pharmacodynamic interactions in DSST (digital symbol substitution test) and RT (reaction time) are noted. All test scores return to base-line after 8 hr of dosing. Because of the variation on PD interaction and safety profile of zaleplon, dose adjustment for zaleplon in insomnia patients is not necessary (Discussed with the medical officer).

Zaleplon with Thioridazine — Thioridazine is a potent inhibitor of oxidative reactions and it also induces sedative hypnotic side effects. Single dose of 50 mg thioridazine does not affect the PK of 20 mg zaleplon, and vice versa. However, additive effect on RT, CFFT, and supra-additive effect on DSST for the first 4 hr after drug administraion are observed when the two drugs are administered together. The effects returned to baseline at 8 hr after drug administration. With higher dose of thioridazine (PDR recommends up to 300 mg), the PD interaction between the two drug could be greater. However, the PD interaction is more determined by thioridazine rather than zaleplon, therefore, dose adjustment for zaleplon is not necessary (discussed with the medical officer).

Ethanol — Single dosing of 10 mg zaleplon and 0.75 g/kg ethanol potentiates each other's effects on simple and complex reaction time, DSST, symbol copying test, and the variability component of the divided attention test. But the impairment is much less than the combination treatment of triazolam and ethanol. As for the benzodiazepines, zaleplon should not be taken with ethanol.

The following drug interactions have been studied by the sponsor and were found to be absent:

Diphenhydramine — Diphenhydramine is a weak AO inhibitor. Single dose of 50 mg diphenhydramine does not affect PK or safety profile of zaleplon (single dosing at 10 mg). Zaleplon does not affect PK of diphenhydramine either.

Paroxetine — Paroxetine, administered for 7 days at 20 mg qd, shows no significant effect on PK or PD (critical flicker fusion threshold, tapping rate, auditory reaction time and DSST) of 20-mg single-dose zaleplon. Neither does zaleplon affect paroxetine steady state concentration.

Digoxin — Single dose of 10 mg zaleplon has no clinically significant effect on PK or PD (ECG recordings) of digoxin dosed at 0.375 mg for 5 or 9 days.

Warfarin — Multiple dosing of zaleplon (20 mg qd for 11 days) has no effect on PK or PD (pro-thrombin time) of single oral dosing of 25 mg warfarin.

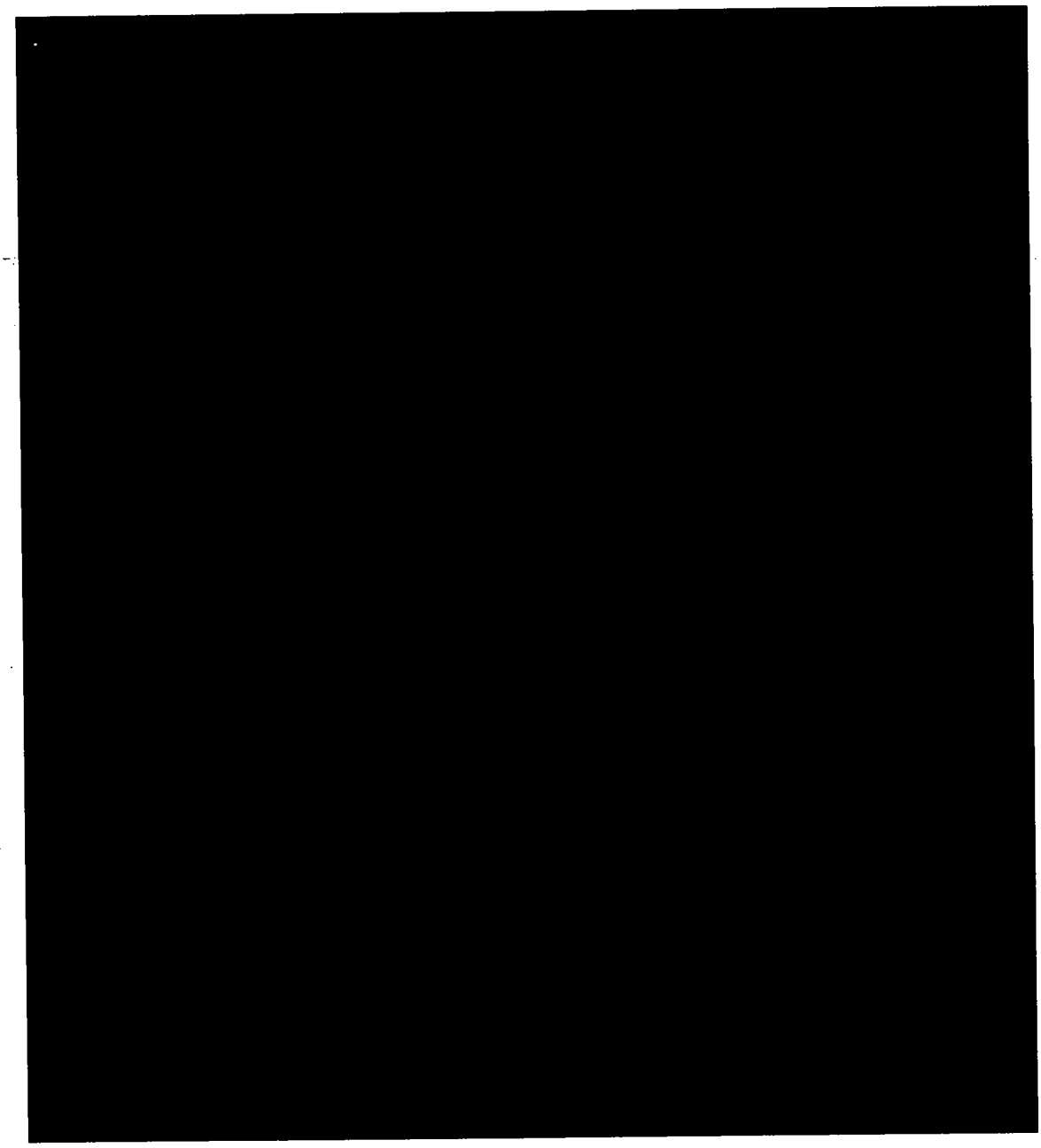
6β-hydroxycorticol/cortisol — Multiple dosing of zaleplon (20 mg qd for 11 days) has no effect on the ratio of 6β-hydroxycorticol/cortisol, indicating zaleplon does not affect CYP3A4 activity.

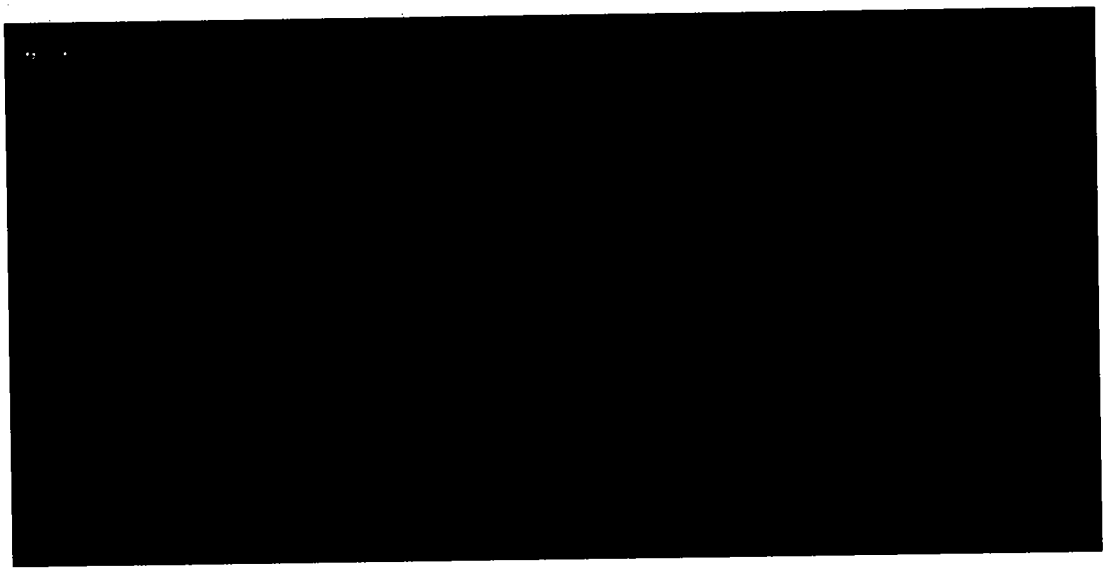
Ibuprofen — No PK interaction has been observed between 10 mg single dose zaleplon and 600 mg single dose ibuprofen, a drug that can severely affect renal function.

BIOPHARMACEUTICS

-Is there an IVIVC developed to support biowaivers ?
-If an ER formulation, how is the target release rate established ?
- How is the performance of the TBM formulation demonstrated ?

Formulation and Dissolution:





Dissolution — Zaleplon is a very weak base with a constant solubility of 0.2 mg/mL over the pH range 1.0 to 9.0. Water is, therefore, chosen as the dissolution medium. During formulation development, three different paddle speeds (50, 75, and 100 RPM) were evaluated. The [redacted] rate exhibited highly variable results, with some cases of incomplete release at [redacted] The [redacted] rate resulted in rapid and complete release of the drug from the capsules; therefore, a profile was difficult to ascertain at [redacted] The [redacted] RPM rate was found to eliminate the mounding of the powder seen at [redacted] while providing a profile that could be used to determine batch-to-batch variability. The sponsor proposes the final dissolution methods and the specifications to be as follows.

Apparatus: **USP Apparatus 2, at** [redacted]
Medium: **900 mL Deionized water, 37 °C**
Sampling Time: [redacted]
Analytical Methods: [redacted]
Recommended Dissolution Specification: [redacted]

However, the individual capsule dissolution profile demonstrates that all the capsule are over [redacted] dissolved at [redacted] under the proposed dissolution methods. Therefore, the specification should be set at [redacted]

Bioequivalence:

[redacted]

The primary comparison was studied for the cross-site formulations (ie, 1 x 10 mg [redacted] vs 1 x 10 mg [redacted], 2x 5 mg [redacted] vs 2x 5 mg [redacted] 2x 5 mg [redacted] vs 1x 10 mg [redacted] n=31). The secondary comparison was studied for within-site capsules (ie, 1x 10 mg [redacted] vs. 2 x 5 mg [redacted], and 2x 5 mg [redacted] VS. 1x 10 mg [redacted] n=31).

In the primary comparison, bioequivalence between **1x10 mg** [redacted] capsule and **1x 10 mg** [redacted] capsules (90% C.I. of Cmax: 93-110; of AUC: 95-104), and between **2x 5 mg** [redacted] capsule and **2x 5 mg** [redacted] (90% C.I. of Cmax: 97-114; of AUC: 100-110) are demonstrated. In the latter comparison, 5 mg [redacted] capsule appears to provide higher concentration than 5 mg [redacted] capsule (point estimate comparison is 105% for both Cmax and AUC). Comparison between 2 x 5 mg [redacted] capsule and 1 x 10 mg [redacted] capsule shows that 2 x 5 mg Gosport capsule provided greater AUC than the 1 x 10 mg [redacted] capsule, but still within the acceptable bioequivalence criteria (90% C.I. of AUC: 100-110). However, comparison of Cmax misses the bioequivalent criteria by a small margin (90% C.I. of Cmax: 108-127).

The secondary comparison for the capsules manufactured at the same site shows that the two [redacted] **capsules were equivalent** (90% C.I. for Cmax: 103-121; for AUC: 96-106). But the two capsules at [redacted] **manufacturing site are not equivalent** on Cmax (90% C.I.: 107-126), though equivalent for AUC (90% C.I.: 101-111). Interesting to note, a significant period effect was also observed for AUC of both formulations administered with 48 hr washout time in the study. Drug levels in the latter periods for either formulations are always lower than that in the first period.

[redacted] *(clinical trial formulation)* --- Bioequivalence between 10 mg capsule and 2 x 5 mg capsules is demonstrated (90% C.I.: 91-114% for Cmax and 91-104% for AUC) for [redacted] formulations in 36 subjects. Using 7 days washout period between treatment, no period effect is observed.

[redacted] *(clinical trial formulation) and* [redacted] *(to-be-marketed formulation)* --- Bioequivalence between 20 mg [redacted] regimen (**1x5 mg + 1x 15 mg**) and 20 mg [redacted] regimen (**2x 10 mg**) has been demonstrated in 32 subjects (90% C.I. of Cmax: 90-103; of AUC: 93-105). As observed in another study, a significant period effect is observed for Cmax and AUC of both formulations administered with 48 hr washout period in this study. The drug levels in the second period for either formulations is always lower than that in the first period, suggesting an induction potential on metabolic enzymes by one or more metabolites that have long elimination half-life. The induction potential after high dose zaleplon administration has been observed in the animals. But considering that in most cases, zaleplon will be used for short-term sleep control and the period effect does not appear consistent, its clinical impact may not be significant.

COMMENTS

1. Food delays the Tmax by 2 hr and decreases Cmax by 36%. Therefore, for a faster on-set sleep effect, zaleplon should be taken without food.

2. In hepatic impairment patients, Cmax of zaleplon increased 2-3 times, and AUC 4-7 times (depending on the severity of liver disease) of the respective value in healthy volunteers. Elimination half-life increased significantly from 1.0 hr in healthy volunteers to 2-3 hr in liver diseased patients. Correspondingly, sleep incidence is higher in the liver impaired patients than healthy volunteers. Therefore, zaleplon should not be used in patients with severe liver disease. In patients with mild and moderate liver disease, initial dose of zaleplon at 5 mg is recommended.

3. With prolonged time of administration (≥10 days), a decreased absorption of the drug has been observed. Because the concentration of the drug seems to be related to the effect of the drug (still under investigation), a delayed effect would be expected after chronic administration of the drug.

4. At a given dose, Japanese population has higher Cmax (by 37%) and AUC (by 70%) of zaleplon than North American or European populations. The reason for this difference is currently being investigated by the OCPB review team. Initial dose of 5 mg is recommended for this population.

5. Zaleplon is excreted into the breast milk. At 10 mg dose, approximately 1.5 ug of the dose is in the breast milk (assuming volume of milk excretion is 100 ml). Assuming that the volume of distribution of a newborn is 0.5 L/kg, the concentrations of the newborn will be 12 ng/mL (assuming 4 kg in weight). Since the safety profile of zaleplon in infants has not been studied, this drug should not be given to nursing women.

6. Rifampicin is a strong CYP3A4 inducer. Dosed at 600 mg qd for 13 days, rifampicin reduces Cmax and AUC of zaleplon to 25% of their respective values. Because of the difficulty in quantitatively assessing the induction effect of rifampicin on zaleplon metabolism at different rifampicin doses, insomnia patients who have been treated by rifampicin should be given an alternative non-CYP substrate hypnotic agent. Similarly, the same consideration should be given to insomnia patients who receive other CYP3A4 inducers, such as phenytoin, carbamazapine, phenobarbital.

7. At 800 mg single dose, cimetidine increases the zaleplon Cmax and AUC by 85% each. At higher dose or multiple dose of cimetidine, it is possible that its effect on zaleplon will be even larger. Therefore, insomnia patients on cimetidine should be given 5 mg zaleplon as the initial dose.

8. The effects of AO inhibitors stronger than cimetidine on zaleplon pharmacokinetics are unknown and should be investigated by the sponsor.

9. The effect of zaleplon on other drugs' pharmacokinetics is unknown, and should be investigated by the sponsor.

10. Single oral dose of impiramine at 75 mg, thioridazine at 50 mg and ethanol at 0.75 g/kg enhance zaleplon pharmacodynamic effects (additive or supra-additive) without affecting its kinetics. Considering most of the PD effects return to baseline at 8 hr after drug administration, and the effects depend more on drugs other than zaleplon, dose adjustment for zaleplon is not necessary but the observation should be included in the labeling.

11. Dissolution methods proposed by the sponsor are acceptable. However, the specification should be changed to NLT [redacted]. We, therefore, propose the following dissolution methods and specification to be adopted by the sponsor: **USP Apparatus II, 900 mL of water at 37 ± 0.5 °C, [redacted] paddle speed, Q=[redacted] at [redacted]**

RECOMMENDATIONS

The sponsor has provided adequate information on the pharmacokineic of zaleplon to support its approval. The sponsor should incorporate the above comments into labeling, and where appropriate, [redacted]

Note: The zaleplon drug interactions with cimetidine, imipramin, digoxin, warfarin and thioridazine were reviewed by Dr. Chandra Sahajwalla.

Primary Reviewer: Rae Yuan, Ph.D /S/ [redacted] 9/24/98

Team Leader: Chandra Sahajwalla, Ph.D /S/ [redacted] 9/24/98

Date of Signature: APPEARS THIS WAY ON ORIGINAL

CC list: HFD-120, HED-860 (Sahajwalla, Malinowski, Yuan), CDR (Barbara Murphy)

STUDY 308

Table 1 (308)

DEMOGRAPHIC AND BASELINE CHARACTERISTICS FOR PATIENTS IN ITT POPULATION
DOUBLE BLIND TREATMENT PHASE

CHARACTERISTICS	ZAL 10 MG (N=145)	ZAL 5 MG (N=139)	PLACEBO (N=138)	p-VALUE
AGE (YEARS), N	145	139	138	
MEAN	72.5	72.5	72.4	0.976 (A)
STANDARD DEVIATION	6.3	5.9	6.8	
RANGE	64 - 91	59 - 90	63 - 95	
SEX, N				
FEMALE	104 (72%)	87 (63%)	94 (68%)	0.251 (B)
MALE	41 (28%)	52 (37%)	44 (32%)	
ETHNIC ORIGIN, N				
BLACK		1 (1%)	1 (1%)	0.548 (B)
WHITE	145 (100%)	138 (99%)	137 (99%)	
WEIGHT (KG), N	145	139	138	
MEAN	68.9	68.5	67.6	0.639 (A)
STANDARD DEVIATION	11.4	10.9	11.8	
RANGE	40 - 103	45 - 97	42 - 96	

NOTE: (A) ANALYSIS OF VARIANCE
(B) FISHERS EXACT TEST

Table 2 (308)

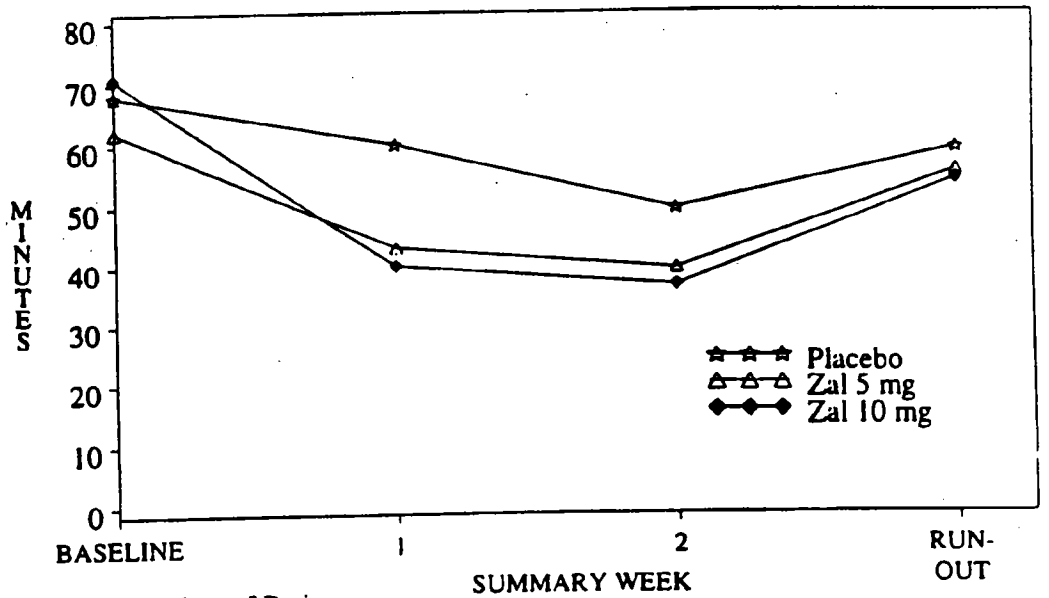
TIME TO SLEEP ONSET (minutes) - ITT POPULATION :
RANKED OBSERVED-VALUE ANALYSIS

Summary Week		Placebo	Zaleplon 5 mg	Zaleplon 10 mg
Baseline	Number of patients	N = 138	N = 139	N = 145
	Median	68.0	62.1	70.7
	IQR	45.0 - 107.1	48.6 - 85.7	46.4 - 102.9
Week 1	Number of patients	N = 137	N = 139	N = 145
	Median	60.0	43.1	40.0
	IQR	35.7 - 85.8	25.7 - 65.7	25.7 - 67.9
	p-Value Dunnett's test		0.001	< 0.001
Week 2	Number of patients	N = 136	N = 129	N = 139
	Median	49.3	39.3	36.4
	IQR	30.0 - 85.4	21.0 - 57.5	22.5 - 57.9
	p-Value Dunnett's test		< 0.001	< 0.001
Run-out	Number of patients	N = 131	N = 129	N = 137
	Median	59.3	55.7	54.3
	IQR	30.0 - 90.0	34.3 - 75.0	35.0 - 90.0
	p-Value Dunnett's test		0.97	0.90

Figure 1 (308)

Median Time to Sleep Onset

Double Blind Intent-to-Treat Population



Group	Number of Patients			
Placebo	138	137	136	131
Zaleplon 5 mg	139	139	129	129
Zaleplon 10 mg	145	145	139	137

Figure 2 (308)

CUMULATIVE DISTRIBUTION OF PATIENTS (308-EU):
TIME TO SLEEP ONSET (MINUTES)