CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020859

MEDICAL REVIEW(S)

MJA

REVIEW AND EVALUATION OF CLINICAL DATA

Addendum to NDA review: review of safety update submitted initially October 26, 1998 without line listings of serious adverse events. Line listings of serious adverse events were submitted October 28, 1998; from this line listing, six cases required further information for review. These six case summaries were submitted November 13, 1998.

Application Information

NDA #:	20-859
Sponsor:	Wyeth Ayerst
Clock Date:	December 31, 1997

Drug Name

Generic Name:	Zaleplon
Trade Name:	Sonata

Drug Categorization

Pharmacological Class:	Pyrazolopyrimidine
Proposed Indication:	Treatment of insomnia (hypnotic)
NDA Classification:	1 S
Dosage Forms:	5 and 10 mg capsules
Route:	Oral

Reviewer Information

Clinical Reviewer:	Paul J. Andreason, M.D.

APPEARS THIS WAY ON ORIGINAL

Summary

Zaleplon is a new chemical entity that is ,currently under review for use as a hypnotic at a recommended dose of 10-20 mg for adults, 65 years old and 5-10 mg for patients over the age of 65 years. The sponsor provides an acceptably complete safety update with these three submissions.

Extent of exposure

Exposure tables were updated for two pools of patients in the zaleplon treatment population. The two pools are designated as groups F and G and correspond to the same group definition in the original NDA 20-859 review. They are:

- **Group F-** Extended-treatment, open-label studies. These studies were used to analyze the safety results from extended treatment with zaleplon. All patients had originally been in parallel- group, placebo-controlled studies. They were either continued on zaleplon or switched from a comparitor or placebo to zaleplon.
- **Group G-** All Phase II/ III studies. This group was used to look at safety data from all patients treated with zaleplon in Phase II and III studies. Group G is comprised of groups D and F. Group D comprised the placebo controlled phase II/III studies.

The original data cut-off dates for patients in the original NDA submission were September 30, 1996 for non-Japanese studies and May 31, 1997 for Japanese studies. Data included in this update comprises patient information from October 1, 1996 to June 30, 1998 for non-Japanese studies and June 1, 1997 to June 30, 1998 for Japanese studies. Exposure tables include tabulations of unblinded data for patients. New patients whose treatment assignment remains blind are not included in exposure tables. Deaths or serious adverse events were reported regardless of whether or not the treatment status was known.

Patients were generally exposed to 5-20 mg/day of zaleplon. There was 0.5 patient years exposure at 2.5-mg/day. Only 34 patients were newly exposed to zaleplon in the non-Japanese studies. These were patients who were randomized to placebo in the double blind treatment phase but who wished to continue in the open label phase on zaleplon. The following table represents non-Japanese exposure to zaleplon in all phase II/II studies until June 30, 1998. Patient-year exposure times for the placebo controlled phase II/III (Group D) studies are included. These exposure times did not change with this safety update, yet they are included to illustrate the amount of patient exposure in

controlled versus uncontrolled studies.

Patient-years of exposure in all non-Japanese phase II/III studies			
Patient Group	**Zaleplon**	**Placebo**	**Comparitor**
Group G (non-Japanese studies)	651.8	39.4	25.9
Group D Zaleplon 2-mg	0.5		
Zaleplon 5-mg	32.1		
Zaleplon 10-mg	55.1		
Zaleplon 20-mg	20.9		
Group D any Zaleplon Dose	108.5		

Patient years of exposure is small in placebo and comparitor groups because these treatments were not available in long-term extension protocols. No new placebo controlled safety data is added to the non-Japanese pool of patients. All additional exposure data since the original NDA submission is from open label extension studies.

Patient years of exposure were not calculated by the sponsor for Japanese studies. Japanese studies were phase II short term studies (7 and 14-day studies) of doses ranging from 5-20-mg/day. Data in this report reflects 57 new patients and 88 patients for whom data was previously behind the blind.

Review of safety data from non-Japanese studies
Since all new and continued exposure data from non-Japanese studies in this submission is from open label studies, safety data was reviewed qualitatively focusing on deaths, serious adverse events, and adverse dropouts. The sponsor provided line listings of patients who either experienced serious adverse events or dropped out of studies due to adverse events. There were no deaths.

Line listings of patients who experienced serious adverse events and who dropped out of studies due to adverse experiences were reviewed. Special focus was placed on events that were not previously reported and potentially related to zaleplon use (e.g. two cases of seizures). Case summaries were requested for seven

cases. All of these cases represented patients who experienced both a serious adverse event and dropped out due the adverse event.

Serious adverse events other than these cases were judged unlikely to be related to zaleplon. Dropouts due to adverse events other than these cases were either unlikely to be related to zaleplon or were adverse events that were previously well characterized in both a qualitative and quantitative fashion in the original NDA.

Seizures

There were two patient reports of seizures in the safety update. **31224-0001 Convulsion-** This was a 39 year-old man who entered the double blind treatment portion of the study 3/3/96 and was randomized to zaleplon 10-mg. He completed the double blind portion of the study on 3/19/96. The patient completed the placebo run-out portion of the study and was assigned to receive open label zaleplon 10-mg on 4/17/96. The does was increased to 20-mg on 4/24/96. On 5/3/97 (open label study day #382) the patient was "taken to an emergency room where he experienced a tonic-clonic seizure." Study drug was discontinued and the patient was placed on phenytoin 200-mg PO BID. At follow-up, the patient reported that he had two closed head injuries as a child that resulted in loss of consciousness and emergency room visits.

31238-0003 Convulsion This was a 53 year old man who was randomized to receive placebo during double blind treatment. He began taking open label zaleplon 10-mg on 12/20/95. On 11/14/96 (open label study day 331) the patient experienced a single seizure with a 10-minute loss of consciousness. He was evaluated at a local emergency room placed on phenytoin and released. Study drug was not discontinued until 11/26/96. The patient had a seizure in November of 1985 and had been treated with phenobarbital from 1985 until 1988. Before the seizure, the patient reported considerable stress, poor nutrition, and the consumption of a quart of beer nightly.

Patient 31238-0003 not only had a previous seizure history but had other factors at work known to decrease seizure threshold. Patient 31224-0001 had two episodes of loss of consciousness as a child resulting in ER visits but apparently no inpatient hospitalization was required. Neither case occurred during a period of abstinence from the zaleplon; both cases occurred after greater than 300 consecutive days of treatment. It is unlikely that either of these cases are related to zaleplon or withdrawal

from zaleplon.

SGOT Increased/ SGPT Increased
There were two cases of SGOT/SGPT increase. No specific etiology was demonstrable in either case, but the only other cases of dropout in the original NDA due to increased LFTs were seropositive for hepatitis C.

31250-0004 was a 44 year-old woman who was assigned to one week of zaleplon 10-mg followed by another week of zaleplon 20-mg during the double blind treatment phase (5/17/96-6/2/96). On 6/14/96 the patient was assigned to receive zaleplon 10-mg which was increased to 20-mg on 6/24/96. SGOT/SGPT were within normal limits and stable during double blind treatment (SGOT 17 then 15; SGPT 27 then 18 at the end of the study).SGOT/SGPT values remained within normal limits (9-34U-SGOT; 6-34U-SGPT) until 9/11/96 where SGOT rose to 37U but SGPT remained normal at 20U. On open label study day 173 (12/3/96) the patient's SGOT/SGPT were 110U and 216U. By 12/5/96 SGOT and SGPT were 27U and 100U. They had returned to normal by 12/13/98 at 19U and 29U respectively. The patient concurrent asthenia, flu symptoms, headaches, nausea and dizziness beginning 11/25/96 with diarrhea and vomiting on 12/2/96. The patient took acetaminophen intermittently throughout the study.

Patient 31250-0004 had symptoms consistent with some form of hepatic/enteric process, possibly a viral infection. Due to the extended treatment period without symptoms or elevated SGOT/SGPT it is unlikely that these events were related to zaleplon.

31221-0006 was a 56 year-old man who received zaleplon 10-mg from 7/18-31/96 during double blind treatment. Values before and after double blind treatment were normal and nearly identical. The patient began open label zaleplon 10-mg on 8/28/96 and increased to 20-mg on 9/4/96. On open label study day 259 the patient had SGOT 27U (WNL) and SGPT 48U (upper limit 43U). The patient continued receiving his last open label dose on 7/31/97. SGOT/SGPT was 217 and 114U respectively. Final values after placebo run-out were 22U and 38U. The patient reported a previous history of asymptomatic increase in liver enzymes. There were no associated physical symptoms or signs.

Patient 31221-0006 represents a case of extended exposure to drug with a short asymptomatic increase of SGOT/SGPT that resolve quickly. The sponsor reports this case as a serious event and a dropout. It appears from the case summary that this patient did

not technically drop out of the study; however, his elevated SGOT/SGPT did resolve within one week of the discontinuation of zaleplon. Rechallenge was not performed. Demonstrable enzyme increase was not present until day 339 of the study. It is unlikely that the enzyme increase was related to zaleplon primarily due to the extended time on drug with no enzyme abnormality.

Hypertension

There was one case of hypertension. Patient 31237-0008 was a 64 year-old man with a prestudy history of hypertension. His screening BP was 150/92 and study day 1 BP was 160/90. The patient reported that he went to an emergency room on 9/15/96 (open label study day 139) and was treated for a "hypertensive crisis" with nifedipine 10-mg. He was discharged from the hospital on nifedipine XL 30-mg. No BP data was available from the ER. Four days after discontinuing zaleplon his BP was 184/90. This episode is unlikely to be related to zaleplon. It predated the use of zaleplon and did not resolve with its discontinuation.

Vertigo

30858-0006 was a 76 year-old woman who began open label treatment with zaleplon 5-mg on 10/15/96. On 10/25/96 she reported vertigo but continued taking zaleplon 5-mg until 12/16/96. Three days later, the vertigo resolved. The sponsor coded most neurological events as serious; however, this event does not meet the usual agency criteria for a serious adverse event. The patient continued and the investigator allowed the patient to continue taking zaleplon for nearly three months in the face of the reported vertigo. The symptom reportedly abated three days after discontinuing the drug. This is a relatively long time based on zaleplon's one hour half-life. It is unclear whether or not this patients vertigo was due to zaleplon. The event should probably be listed in the narrative section of the adverse events section of labeling as it was the cause of dropout in 4/2069 patients in the original NDA.

Agitation/Confusion/Delirium

30841-0108 was a 72 year-old man with a past history of alcoholism (in remission for two years). On May 30, 1996 he received zaleplon 10-mg in double blind therapy. On June 20, 1996 he was assigned to open label zaleplon 5-mg after successfully completing the placebo washout. On July 4, 1996 the patient had a family conflict after which he drank a large amount of alcohol. He experienced sweating, nausea, vomiting and "inner

restlessness". He was dropped from the study and admitted to the hospital on July 8, 1996 due to "pre-delirium". He recovered with conservative treatment and was discharged from the hospital on August 1, 1996.

This set of symptoms was most likely due to heavy alcohol use in a patient who was abusing alcohol in association with a psychosocial stressor. It is unlikely that zaleplon is related to the events in this case.

Review of safety data of Japanese studies
Japanese studies were reviewed qualitatively focusing on deaths, serious adverse events, and adverse dropouts. The sponsor reported no new deaths or serious adverse events in these Japanese studies. There were six dropouts due to adverse events. Five of these adverse dropouts were due to somnolence or dizziness. These adverse events were observed and characterized in the original NDA and no further review is required of these cases. The remaining Japanese adverse dropout was a 32 year old female who dropped out due to "enlarged abdomen". This was unlikely related to zaleplon.

Conclusions and Recommendations
This safety review reports two events that can not be causally linked to zaleplon yet have not heretofore been reported. Those events are elevated SGOT/SGPT in the absence of viral hepatitis and seizures.

Seizures were a prominent finding in the animal toxicology studies yet were not seen in humans. Seizures in animals were considered due to withdrawal. Though both of these patients had medical histories that increased their risk for seizures, it can not be concluded that zaleplon contributed to the occurrence of the seizures in any way. The seizures occurred during periods when both patients were actively taking the drug; however, the half-life of zaleplon is so short that withdrawal, were it to occur, could start many hours prior to the next scheduled dose. I recommend that these two events be mentioned in the narrative portion of the adverse event section in labeling.

The two episodes of increased SGOT/SGPT can not be causally linked to zaleplon yet they lack a defined etiology. Both cases resolved with an associated discontinuation of zaleplon. Zaleplon was not administered again to these patients. I recommend that these events be mentioned in the narrative section of the adverse events section in labeling.

I likewise recommend that vertigo be mentioned in the narrative section of the adverse events section of labeling.

The reported case of hypertension appears in no way connected to zaleplon. It preceded treatment and continued after discontinuation recommend that this event not be mentioned in labeling.

The case of agitation, delirium, and confusion is unlikely to be related to zaleplon. Hypnotic agents may be related to symptoms of confusion and agitation in patients who are elderly, demented, or have idiosyncratic reactions to alcohol. Symptoms of hallucinations, memory loss, and lack of coordination were reported in the original NDA, but this case adds nothing new to the safety database.

/S/ [redacted] 11/25/98

Paul J. Andreason, M.D.

cc: NDA 20-859
HFD-120
HFD-120/PAndreason
TLaughren
MMille

8-5-99

We met with WS on 8-4-99 to discuss final labeling. We worked up comments on final labeling, including the mention of the 2 cases of seizure in the Drug Abuse & Dependence section. NDA can now be approved. See my approval memo for more detailed regulatory comments.

/S/ [redacted]

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

DATE: November 10, 1998 /S/ [redacted]

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approvable Action for
Sonata (zaleplon)

TO: File NDA 20-859
[**Note:** This overview should be filed with the 12-30-97
original submission.]

1.0 BACKGROUND

Zaleplon is a nonbenzodiazepine gaba-agonist that is being proposed for use as a hypnotic. The sponsor argues that zaleplon has the following advantages compared to other available hypnotic drugs: minimal next day sedation; no daytime anxiety; minimal memory impairment; minimal tolerance; and minimal rebound insomnia and other withdrawal effects.

IND [redacted] for zaleplon [redacted] Several critical meetings were held during the development of zaleplon:

12-14-93: This was the initial end-of-phase 2 meeting.
-We discussed the program to date and agreed that the sponsor was ready to proceed with phase 3.
-Several issues were discussed:

-The sponsor indicated that they planned to study zaleplon for treatment of early morning insomnia, and we cautioned them that this was a controversial topic requiring much thought and planning.

-The sponsor indicated that they planned to include active comparators, and we clarified that the purpose was for assay sensitivity rather than to support comparative claims.

-We indicated that it would be important to carefully evaluate for potential withdrawal effects.

-Several pharm/tox issues were discussed and were identified as subjects for ongoing negotiations.

11-17-95: This was a second end-of-phase 2 meeting.
-A second EOP-2 meeting was held, since a new sponsor had acquired the product and wanted feedback on an expanded phase 3 program. We indicated that they were fairly far along in development, but had several comments:

-We indicated that they would need to do at least 1 study in transient insomnia.
-They had excluded patients with hepatitis in earlier studies, and we suggested they should now include such patients, otherwise they would have no experience in this population.

5-7-97: This was a pre-NDA meeting.
-This was a technical meeting focused predominantly on formatting of the NDA and the planned CANDA. We gave extensive feedback on the clinical issues pertinent to the planned NDA, both safety and efficacy, and offered to work with them more informally to ensure that the NDA would meet our requirements.

The original NDA 20-859 for zaleplon was submitted 12-30-97. A safety update was submitted 10-22-98 and a review is pending.

We decided not to take zaleplon to the Psychopharmacological Drugs Advisory Committee (PDAC).

2.0 CHEMISTRY

A CMC deficiency letter has been sent and the resolution of several minor issues is pending. However, I am not aware of any CMC issues that would preclude the approval of this drug.

3.0 PHARMACOLOGY

Zaleplon is a gaba agonist with pharmacological properties similar to other sedative/hypnotic drugs. There were several positive findings in toxicity studies, including liver adenomas in female mice and clastogenicity findings in two genotoxicity assays. While there were no findings of teratogenicity, there were findings suggestive of increased fetal deaths and growth effects. None of the findings would be sufficient to preclude the approvability of zaleplon, but will be noted in labeling. We have extensively modified the sponsor's proposed pharmacology/toxicology sections of labeling. I am not aware of any pharmacology/toxicology issues that would preclude the approval of this drug.

4.0 BIOPHARMACEUTICS

The pharmacokinetics of zaleplon have been adequately characterized and there are no pharmacokinetic deficiencies that would preclude the approvability of this drug. We have made a number of changes to the pharmacokinetics sections of proposed labeling. We will propose dissolution specifications in the approvable letter.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

There were a total of 13 fixed dose studies pertinent to the claim of effectiveness in reducing either latency to persistent sleep (LPS) or time to sleep onset (TSO), including 8 sleep lab studies utilizing polysomnographic (PSG) recordings and 5 outpatient studies utilizing patient diaries. All but 2 of these studies involved subjects with what could reasonably be considered primary insomnia; the remaining 2 studies (209 and 210) represented models of what could be considered transient insomnia. Table 1 (appendix) summarizes the populations studied, treatment sequences, doses, and durations for these studies.

In all but 1 of these studies, the protocol identified primary outcome variable was either latency to persistent sleep (LPS), as measured by PSG, or time to sleep onset (TSO), as assessed by patient diary; the exception was study 209, a sleep lab study utilizing a phase advance model of transient insomnia, in which 2 primary outcomes were identified, including both LPS and sleep efficiency. Since these studies were focused on demonstrating an effect on either LPS or TSO, the reviews done by Dr. Paul Andreason from the clinical group and Dr. David Hoberman from the biometrics group focused on these outcomes, despite the fact that other outcomes were also collected. I will also focus only on LPS or TSO, and I consider the other findings are largely irrelevant to the decision regarding this NDA and also to labeling.

In Table 2 (appendix), I have summarized the significance levels (2-sided) for pairwise comparisions (zaleplon vs placebo) for the dose groups pertinent to the dosing recommendations for this drug, i.e., 5 to 10 mg for elderly adults and 10 to 20 mg for nonelderly adults. It should be noted that, by statistical plan, these were comparisons of raw mean scores for each group vs placebo at the time points in question, i.e., there were no corrections for baseline differences in values. In Table 3 (appendix) I have summarized the effect sizes for these studies, using the difference between each dose group and placbo in raw mean score for either LPS or TSO as a measure of effect.

In summary, this array of studies substantially supports the effectiveness of zaleplon in reducing LPS or TSO at a dose of 5 mg in the elderly and 10 mg in nonelderly adults. In addition, there was a suggestion from the data that the next highest dose studied in the nonelderly patients, i.e., 20 mg,

may have been slightly more effective. The data from the outpatient studies supported the effectiveness of zaleplon out to 28 days of treatment. Subgroup analyses based on gender did not suggest any differential responsiveness based on this factor.

In conclusion, this program, utilizing both sleep lab studies and outpatient studies, provided support for the effectiveness of zaleplon in reducing LPS or TSO for periods of up to 28 days.

5.2 Safety Data

5.2.1 Clinical Data Sources for Safety Review

The safety data for zaleplon, including the original submission and the amendments in response to our requests for additional information, were reviewed by Dr. Paul Andreason (reviews dated 7-14-98 and 7-27-98). This original review was based on an integrated database (with a cutoff date of 9-30-96 for both the integrated database and also for deaths and other serious events).

Approximately 5000 human subjects were exposed to zaleplon in the sponsor's development program (in the integrated database, plus the Japanese experience), including 904 in phase 1 studies and 4105 in phase 2-3 studies. Only deaths, serious adverse events, and adverse dropouts were available for approximately 400 Japanese patients exposed to zaleplon. The total person-time for zaleplon-exposed patients in the non-Japanese phase 2-3 program was approximately 450 person-years. Patients in phase 2-3 studies were roughly 60% female and predominantly white. Approximately 2/3 of the roughly 3000 patients in placebo-controlled phase 2-3 trials were in an 18-64 year-old range, and approximately 1/3 were > 65, so the experience in elderly patients was quite substantial. For nonelderly adults, the usual zaleplon doses were either 10 or 20 mg, while for elderly adults the usual dose was 5 mg. While most of the zaleplon experience was relatively short-term, there were 263 patients exposed for $\geq$ 6 months and 31 patients exposed for $\geq$ 12 months.

5.2.2 Adverse Event Profile for Zaleplon

5.2.2.1 Overview

There would not be acceptance of a hypnotic that was associated with significant adverse effects, and in fact, based on what we have, zaleplon appears to be relatively free of effects other than those anticipated from a short-half life sedative/hypnotic drug. I will discuss in the next section (5.2.2.2) in more detail how zaleplon looks regarding the profile of acute, next-day, and withdrawal effects of concern for drugs in this class, however, otherwise it is difficult to distinguish this drug from placebo in terms of unwanted effects. The 1 death reported was a suicide in a Japanese patient who was actually off zaleplon and taking zolpidem at the time. There was no difference between zaleplon and placebo in the overall rate of dropout for adverse events. The most frequent reasons for dropout among zaleplon-exposed patients were dizziness, headache, and somnolence, however, again, it was difficult to distinguish zaleplon from placebo regarding specific events leading to dropout. Serious events reported for zaleplon that could be reasonably attributed to zaleplon were hallucinations,

amnesia, and depression, and these will be discussed in the next section. There were 3 reports of dizziness, 2 mild and self-limited, and 1 more significant, but occurring in a patient who insisted on remaining up and about after taking his zaleplon. Overall, when comparing all spontaneously reported adverse events for zaleplon and placebo, the rates for individual events were generally comparable, and none met our criteria for common and drug-related (i.e., incidence of 5% and twice the placebo rate). A dose-response analysis for the 28 day studies revealed an association for 3 events, i.e., headache, amnesia, and hypesthesia; certainly for amnesia, this is a plausible relationship, but the other two are likely chance associations. There was no clear indication of any zaleplon-related laboratory, vital signs, or ECG abnormalities. [Note: The ECG analysis is based on 2 small, phase 1 studies, however, there is no indication from these studies of any ECG effect, and no indication from animal studies of an ECG effect. Thus, I agree with Dr. Andreason that this is sufficient.] There were 2 reported, relatively small, overdoses, both associated with the expected picture of excessive sedation, and full recovery.

5.2.2.2 Adverse Events of Particular Concern for Sedative/Hypnotic Drugs

There are a number of adverse events that have been reported for other hypnotic drugs and are of concern, and I will comment in this section on the extent to which these events were assessed for and observed in association with zaleplon use. I will also comment on the sponsor's handling of these events in their proposed labeling, and I will discuss my preferred alternative approaches in certain cases.

5.2.2.2.1 Acute Effects

Clearly, the sought after acute effects of hypnotics are decreased sleep latency and improved sleep maintenance. The clinician's hope and expectation is that a patient will attempt to sleep immediately upon taking a sleeping pill; unfortunately, patients often delay their attempts to sleep after taking a sleeping pill, resulting in an opportunity for other acute, nondesireable, effects to emerge, e.g., memory impairment, psychomotor impairment, and other psychiatric/behavioral phenomena, e.g., hallucinations. These effects may also emerge in patients who awaken for whatever reason during the period of pharmacological activity for a hypnotic. Other acute pharmacological effects that may be associated with hypnotic use include respiratory depression and alteration of the normal architecture of sleep, i.e., sleep stages.

5.2.2.2.1.1 Acute Memory Effects

There were 4 studies pertinent to acute memory effects of zaleplon, i.e., 103, 108, 122, and 143 (see Andreason 7-14-98 review, pp. 72-76). These were all single dose studies looking at memory and sedative/psychomotor effects of different doses of zaleplon and other hypnotics vs placebo in healthy subjects.

-Study 103 involved the assessment of subjects at 1 hour after dosing, and not surprising, both 10 and 20 mg of zaleplon were associated with impairments on tests of memory and psychomotor function, compared to placebo and zaleplon 5 mg.

-Study 108 involved only a 20 mg zaleplon dose, and assessed subjects at 1, 3, and 5 hours after dosing. Not surprising, zaleplon 20 mg was associated with impairments on tests of memory and psychomotor function compared to placebo at 1 hour, however, these differences were gone by 3 hours.
-Study 122 involved 10 and 20 mg zaleplon doses, and assessed subjects at 1.25 and 8.25 hours after dosing. In this study, zaleplon 10 mg was not distinguishable from placebo on tests of memory or psychomotor function, however, zaleplon 20 mg was associated with impairments on tests of memory and psychomotor function compared to placebo at 1.25 hours, but not 8.25 hours.
-Study 143 involved only a zaleplon 10 mg dose vs placebo, and was designed to look at memory and psychomotor function to subjects upon awakening after a full nights sleep when dosed with a hypnotic at 5, 4, 3, and 2 hours prior to finally awakening. It seems to me that the 2 hour dosing is relevant to the question of acute effects, and it was of interest that dosing with zaleplon at 2 hours before awakening was not distinguishable from placebo on tests of memory or psychomotor function.
-Comment: While not entirely consistent, these studies show the expected result that zaleplon, at doses of 10 mg and 20 mg, causes impairment of memory and psychomotor function at 1 hour, i.e., the time at which it would be expected to have its peak pharmacological effect. Consistent with its rapid clearance, these effects appear to have largely subsided as early as 2 hours post-dosing. The sponsor wishes to focus in labeling only on the negative finding for zaleplon 10 mg in study 122 regarding acute memory and psychomotor effects, ignoring the positive findings for both this and the other 2 studies (see WA 12-30-97 labeling, p. 2). This is unacceptable, and I have proposed a more balanced summary of the acute memory and psychomotor effects.

5.2.2.2.1.2 Acute Sedative/Psychomotor Effects

The same studies summarized in the previous paragraph regarding acute memory effects are also pertinent to the quesion of acute psychomotor effects, since, as noted, they also included measures of psychomotor function, and the findings for psychomotor function were identical to those for memory. I have also provided a more balanced summary statement for acute psychomotor effects in labeling than that proposed by the sponsor.

5.2.2.2.1.3 Acute Psychiatric/Behavioral Phenomena

Sedative/hypnotic drugs have been associated with a variety of acute psychiatric/behavioral phenomena, often characterized by decreased inhibition, e.g., uncharacteristic aggression or extroversion. In addition, these drugs have been reported to be associated with bizarre behavior, agitation, hallucination, depersonalization, and depression. Of these events, only hallucinations have been clearly associated with zaleplon use acutely.
Hallucinations: Hypnagogic, generally visual, hallucinations were an infrequent, self-limited, event, occurring at an incidence of roughly 0.5% for both zaleplon and placebo (see Andreason 7-14-98 review, pp. 43-47).

Hostility: There was only 1 report of aggressiveness, i.e., a patient felt aggressive and irritable on the morning after taking zaleplon 10 mg (see Andreason 7-14-98 review, pp. 43-47). There was also a report of aggressiveness in a placebo patient.

-Comment: The sponsor's proposed labeling has a standard Warning statement about the potential for such effects.

5.2.2.2.1.4 Acute Respiratory Depression

There were 3 studies pertinent to acute respiratory effects of zaleplon (see Andreason 7-14-98 review, p. 76): 112 (healthy men); 120 (patients with COPD); and 133 (patients with moderate obstructive sleep apnea). There was no evidence from these studies of any effects of a 10 mg zaleplon dose on blood gases or any other measures of respiratory function.

-Comment: The sponsor has adequately summarized this information and, nonetheless, proposed cautionary language for labeling; I agree (see WA 12-30-97 labeling, p. 9).

5.2.2.2.1.5 Acute Effects on Sleep Stages

There were 3 studies pertinent to acute effects of zaleplon on sleep architecture (see Andreason 7-14-98 review, pp. 76-77), i.e., studies 203, 204, and 205.
-Study 203, involving zaleplon doses of 5 and 10 mg, was apparently not analyzed regarding effects on sleep architecture, and therefore, no conclusions can be drawn regarding this study, despite the sponsor's statement that no important differences were seen. Even if there were analyses of the effects on sleep stages, the results would be difficult to interpret, since study 203 did not reveal any effects of zaleplon on the primary outcome, LPS, beyond the first 2 nights. Thus, it may also not have been sufficiently sensitive to detect drug effects on sleep architecture.
-Study 204 also failed to distinguish zaleplon from placebo on LPS at time points beyond the first 2 nights, and so is difficult to interpret.
-Study 205, a small study comparing 4 zaleplon doses (2, 5, 10, and 20 mg) with placebo, did not show an effect on sleep stages for any of the doses, but also was not consistently effective on LPS. Thus, this study is also difficult to interpret.

-Comment: Given the difficulty in interpreting the data from these studies at later time points, I don't think any summary statements can be made about the effects of zaleplon on sleep stages (see WA 12-30-97 labeling, p. 6).

5.2.2.2.2 Next-Day Residual Effects

Beyond knowing about acute adverse effects of sedative/hypnotics occurring during peak exposure, it is important to know if there are any carryover effects into the next day. Clearly, the extent to which this is a problem depends largely on the elimination half life of a drug in this class. Given the

very short half-life for zaleplon, it would not be expected to be associated with next-day residual effects.

5.2.2.2.2.1 Next-Day Memory Effects

There were 4 studies pertinent to next-day memory effects of zaleplon, i.e., 108, 122, 134, and 143 (see Andreason 7-14-98 review, pp. 72-76). Three of these were single dose studies looking at memory and sedative/psychomotor effects of different doses of zaleplon and other hypnotics vs placebo in healthy subjects. Study 134 looked at memory and driving ability.

-Study 108 involved only a 20 mg zaleplon dose, and assessed subjects at 1, 3, and 5 hours after dosing. As noted under 5.2.2.2.1.1, the impairments in memory and psychomotor function associated with zaleplon 20 mg at 1 hour were gone by 3 hours.

-Study 122 involved 10 and 20 mg zaleplon doses, and assessed subjects at 1.25 and 8.25 hours after dosing. As noted under 5.2.2.2.1.1, zaleplon 10 mg was not distinguishable from placebo on tests of memory or psychomotor function, however, zaleplon 20 mg was associated with impairments on tests of memory and psychomotor function compared to placebo at 1.25 hours, but not 8.25 hours.

-Study 134 involved 10 and 20 mg zaleplon doses, and assessed subjects at 5 and 10 hours after dosing on measures of memory and driving ability. Neither zaleplon dose was associated with impairment on any of these measures at either time point.

-Study 143 involved only a zaleplon 10 mg dose vs placebo, and was designed to look at memory and psychomotor function to subjects upon awakening after a full nights sleep when dosed with a hypnotic at 5, 4, 3, and 2 hours prior to finally awakening. None of these dosings with zaleplon, i.e., at 5, 4, 3, or 2 hours before awakening was associated with next-day impairment.

-In addition to these formal studies of next-day memory and psychomotor impairment, there were also spontaneous reports of memory problems in patients from the clinical trials that are of some interest. While it was not clear in every case whether the amnesia was an acute phemonenon immediately following dosing or later-occurring, several cases clearly were next-day events. Also of interest, there appeared to be a dose-response relationship relationship for amnesia, with a proportionately greater incidence at the 20 mg dose.

-Comment: The formal study results are consistent with the view that zaleplon at clinically relevant doses is not associated with next-day memory impairment. However, the spontaneous reports suggest that, especially at higher than recommended doses, next-day amnesia may occur with zaleplon use. I have proposed labeling language that reflects this view.

5.2.2.2.2.2 Next-Day Residual Sedative/Psychomotor Effects

The same studies summarized in the previous paragraph regarding next-day memory effects are also pertinent to the quesion of next-day psychomotor effects, since, as noted, they also included measures of psychomotor function, and the findings for psychomotor function were identical to those for memory. I have proposed labeling language that reflects this view.

5.2.2.2.2.3 Next-Day Depression/Suicidality and Other Psychiatric/Behavioral Phenomena

Various psychiatric/behavioral phenomena have also been reported as inter-dosing events in association with sedative/hypnotic drug use, so it was of interest to search for the occurrence of such events for zaleplon. One such event reported was depression, i.e., 1 completed suicide in a Japanese patient and 3 reports of mild depression (out of roughly 2800 patients exposed to zaleplon in phase 2-3 studies) that resolved quickly upon discontinuation of zaleplon. There were no similar reports among active comparator or placebo patients. The Japanese patient who committed suicide was actually 4 days post zaleplon use and was taking zolpidem at the time. In addition, 1 patient reported depersonalization and another reported "abnormal thinking."

-Comment: The sponsor's proposed labeling has a standard Warning statement about the potential for such effects.

5.2.2.2.3 Withdrawal Phenomena

5.2.2.2.3.1 Same Night Anxiety/Insomnia

The sponsor cites study 204 as support for a labeling statement that zaleplon was not associated with increased wakefulness during the last quarter of the night after 28 days of treatment (see WA 12-30-97 labeling. p.5). However, Dr. Andreason indicates (see Andreason 7-27-98 review, p. 11) that the data do not support that statement. In addition, as noted previously, this study was not able to distinguish zaleplon from placebo on the primary outcome, LPS, beyond 1-2 nights, and so, would also not likely have been sensitive enough to detect rebound insomnia during the latter part of the night.

-Comment: The data from study 204 do not support the sponsor's labeling claim of an absence of zaleplon-related wakefulness during the latter part of the night during ongoing treatment, and I have indicated in labeling that there are insufficient data to address this issue. .

5.2.2.2.2.2 Next-Day Anxiety

There were 4 studies pertinent to next-day anxiety effects of zaleplon, i.e., 203, 204, 301, and 303 (see Andreason 7-14-98 review, pp. 58-62). These were all placebo-controlled parallel group studies of nonelderly adults with primary insomnia and involved fixed doses of zaleplon. 203 and 204 were sleep lab studies, while 301 and 303 were outpatient studies that utilized patient diaries. 203 was 14 nights, and the rest were all 28 nights.

-Study 203, involving zaleplon doses of 5 and 10 mg, found no drug-placebo differences in the State/Trait Anxiety Index, administered during the days following night-time dosing.

-Study 204, involving zaleplon doses of 10 and 20 mg, found no drug-placebo differences in the Zung Self-Rating Anxiety Scale, administered on the day after the last nightly dose.

-Another measure of daytime emergent anxiety during ongoing treatment comes from a pooled analysis of spontaneously reported anxiety for group D (all the parallel group, placebo controlled

studies: 203, 204, 205, 301, 303, 306, 307, and 308). In this pooled analysis, there was no difference between zaleplon and placebo in spontaneously reported daytime anxiety.

-Comment: The data from these studies support the sponsor's labeling claim of an absence of zaleplon related daytime anxiety during ongoing treatment.

5.2.2.2.2.3 Subsequent-Night (Rebound) Insomnia

There were 7 studies pertinent to rebound insomnia effects of zaleplon, i.e., 203, 204, 301, 303, 306, 307, and 308 (see Andreason 7-14-98 review, pp. 58-60). These were all placebo-controlled parallel group studies of adults with primary insomnia and involved fixed doses of zaleplon. 203 and 204 were sleep lab studies, while the rest were outpatient studies that utilized patient diaries. These studied varied in duration from 14 to 28 nights. Rebound was operationally defined as a temporary worsening in sleep parameters (latency, total sleep time, and number of awakenings) following discontinuation compared to baseline. The analyses looked at both nights 1 and 2 following discontinuation.

Overall, there appears to be both objective (PSG) and subjective (diary) evidence for worsened sleep the first night after discontinuing treatment with zaleplon, and it appears to be dose dependent. However, the rebound effect also appears to be resolved by the second night following withdrawal.

-Comment: The sponsor has reached a somewhat different conclusion in their proposed labeling regarding rebound (see WA 12-30-97 labeling, p. 7), in that they suggest there is no objective evidence for rebound and minimal subjective evidence. I have proposed a rebound statement consistent with our interpretation of the data.

5.2.2.2.2.4 Other Withdrawal Phenomena

The potential for other withdrawal phenomena was assessed for in 14 to 28 day studies in patients with primary insomnia, including both the sleep lab studies (203 and 204) and the outpatient studies (301, 302, 303, 304, 306, and 308). (see Andreason 7-14-98 review, pp. 60-62) Of particular interest was the use of the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ) in several of these studies, both at baseline and then during days 1 and 2 following discontinuation. Withdrawal was operationally defined as the emergence of 3 or more new symptoms after discontinuation. Zaleplon was not distinguishable from placebo at doses of 5, 10, or 20 mg on this measure. Nor was zaleplon distinguishable from placebo on spontaneously reported withdrawal emergent adverse events. There were no instances of withdrawal seizures, delirium, withdrawal associated hallucinations, or any other manifestations of severe sedative/hypnotic withdrawal.

5.2.2.2.4 Tolerance/Dependence/Abuse Potential

Tolerance

The 3 28-day studies in patients with primary insomnia are pertinent to the question of tolerance. These included a sleep lab study (204) and 2 outpatient studies (301 and 303). In the 2 outpatient studies, the beneficial effects on sleep latency persisted throughout the 4 weeks of observation, suggesting that tolerance was not occurring, at least during this observation period. However, in the sleep lab study (204), LPS was decreased compared to placebo only on nights 1-2; there was no effect at later timepoints.

Dependence

Physical dependence is established by the occurrence of a withdrawal syndrome upon discontinuation of a chronically administered drug, and, as noted under 5.2.2.2.2.3 and 5.2.2.2.2.4 above, this potential was assessed for in 14 to 28 day studies in patients with primary insomnia, and was not detected, except for mild rebound insomnia on the first night post-withdrawal.

Abuse Potential

There were 2 studies pertinent to abuse potential for zaleplon, i.e., 104 and 110 (see Andreason 7-14-98 review, pp. 77-78).

-Comment: These studies in subjects with histories of sedative hypnotic abuse revealed that zalelpon, has an abuse potential similar to benzodiazepine and other benzodiazepine-like hypnotics.

5.2.2.2.5 Drug Interactions

5.2.2.2.5.1 Drug-Disease Interactions

Except for pk studies in subjects with renal or hepatic impairment, there were no systematic attempts to explore for drug/disease interactions. A decreased clearance of zaleplon was found for hepatically impaired but not renally impaired patients.

5.2.2.2.5.2 Drug-Drug Interactions

Not surprising, zaleplon potentiates the sedative/hypnotic effects of other drugs, e.g., ethanol, imipramine, and thioridazine. It may be expected that potent inducers of 3A4 metabolism, e.g., rifampicin, may reduce the effectiveness of zaleplon, and potent inhibitors of both aldehyde oxidase and 3A4, e.g., cimetidine, may increase the somnolent effects of this drug. These concerns have been noted in proposed labeling.

5.2.2.3 Conclusions Regarding Safety of Zaleplon

Overall, the adverse event profile for zaleplon is what would be expected for a short half-life sedative/hypnotic, and there are no findings that would preclude the approval of this drug for the treatment of insomnia.

5.3 Clinical Sections of Labeling

We have substantially rewritten the clinical sections of the draft labeling that is included with the approvable letter. The explanations for the changes are provided in bracketed comments in the draft labeling.

6.0 WORLD LITERATURE

Dr. Andreason reviewed the published literature for zaleplon included in the NDA and did not discover any previously unrecognized important safety concerns for this drug. We will ask for a literature update in the approvable letter.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, zaleplon is not marketed anywhere at this time. We will ask for an update on the regulatory status of zaleplon in the approvable letter.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this application to the PDAC.

9.0 DSI INSPECTIONS

At the time of this memo, I am not aware of the results of any DSI inspections of key studies in this development program. This issue will need to be addressed before any final action can be taken for this application.

10.0 LABELING AND APPROVABLE LETTER

10.1 Final Draft of Labeling Attached to Approvable Package

Our proposed draft of labeling is attached to the approvable letter. As noted, we have made substantial changes to the sponsor's draft dated 12-30-97.

10.2 Foreign Labeling

Zaleplon is not marketed anywhere at this time.

10.3 Approvable Letter

The approvable letter includes draft labeling and requests for a safety update, a literature update, and a regulatory status update.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Wyeth-Ayerst has submitted sufficient data to support the conclusion that zaleplon is effective and acceptably safe as a hypnotic. I recommend that we issue the attached approvable letter with our labeling proposal and the above noted requests for updates, in anticipation of final approval.

cc:
Orig NDA 20-859 (Sonata/zaleplon)
HFD-120
HFD-120/TLaughren/PLeber/PAndreason/TWheelous
HFD-100/RTemple

DOC: MEMZLHYP.AE1

Table 1 Efficacy Studies[1]						
Study Number	Population		Study Design			
	Age	Diagnosis	Setting	Sequence	Zaleplon Doses	Duration
201	Adult	1^0 Insomnia	Sleep Lab	Crossover	10,40	2 nights
202	Adult	1^0 Insomnia	Sleep Lab	Crossover	20,60	2 nights
203	Adult	1^0 Insomnia	Sleep Lab	Parallel Groups	5,10	14 nights
204	Adult	1^0 Insomnia	Sleep Lab	Parallel Groups	10,20	28 nights
205	Adult	1^0 Insomnia	Sleep Lab	Parallel Groups	2,5,10,20	5 nights
207	Elderly	1^0 Insomnia	Sleep Lab	Crossover	2,5,10	2 nights
209	Adult	Transient	Sleep Lab	Crossover	5,10	1 night
210	Adult	Transient	Sleep Lab	Parallel Groups	5,10	1 night
301	Adult	1^0 Insomnia	Outpatient	Parallel Groups	5,10,20	28 nights
303	Adult	1^0 Insomnia	Outpatient	Parallel Groups	5,10,20	28 nights
306	Elderly	1^0 Insomnia	Outpatient	Parallel Groups	5,10	14 nights
307	Adult	1^0 Insomnia	Outpatient	Parallel Groups	10,20	14 nights
308	Elderly	1^0 Insomnia	Outpatient	Parallel Groups	5,10	14 nights

1 All studies were randomized, double-blind, and placebo-controlled

Table 2
Efficacy Results for Zaleplon vs Placebo
Summary of Significance Levels[1] (2-sided) for Pairwise Comparisions (Zaleplon vs Placebo)[2] in Observed Cases (OC) analyses[3] of Time to Sleep Onset (TSO) or Latency to Persistent Sleep (LPS)[4]

Study Number/Dose Group	Study Night[5]						
	1	2	5	7	14	21	28
201: 10 mg[6]		*					
202: 20 mg[7]		*					
203: 10 mg[8]		*			-		
204: 10 mg[9]		*			-		-
204:20 mg		*			-		-
205: 10 mg[10]		*	-				
205: 20 mg		*	*				
207: 5 mg[11]		*					
207: 10 mg		*					
209: 10 mg	-						
210: 10 mg	*						
301: 10 mg				*	-	*	t
301: 20 mg				*	*	*	*
303: 10 mg				*	*	*	*
303: 20 mg				*	*	*	*
306: 5 mg				-	*		
306: 10 mg				*	*		
307: 10 mg				*	*		
307: 20 mg					*		
308: 5 mg				*	*		
308: 10 mg				*	*		

1 Based on ANCOVA
* = $p \leq 0.05$
t = $p \leq 0.10$
- = $p > 0.10$

2 Results are presented separately for the following dose groups: 10 and 20 mg for nonelderly adults, and 5 and 10 mg for elderly adults, since these are the dose groups pertinent to dosing recommendations for zaleplon. Results for other dose groups are not presented. The statistical results are based on comparisons of raw means; by statistical plan, there was no correction for baseline differences. Significance levels presented in this table have been adjusted for multiple dose groups in the individual studies.

3 Only observed cases (OC) results are provided; last-observation-carried-forward (LOCF) results were almost always comparable.

4 Latency to persistent sleep onset (LPS) was always identified as the sole primary outcome for sleep lab studies, except for study 209, in which case there were two primary outcomes, including LSP. The p-values for LSP for that study were adjusted for these 2 outcomes as well as for multiple dose groups. Time to sleep onset (TSO) was always identified as the sole primary outcome for the outpatient studies.

5 The assessments were based on either polysomnographic recordings in sleep lab studies or on patient diaries completed on the mornings after dosing.

6 For study 201, the night 2 result refers to a mean of nights 1-2.

7 For study 202, the night 2 result refers to a mean of nights 1-2.

8 For study 203, the night 2 result refers to a mean of nights 1-2, and the night 14 result refers to a mean of nights 13-14.

9 For study 204, the night 2 result refers to a mean of nights 1-2, the night 14 result refers to a mean of nights 13-14, and the night 28 result refers to a mean of nights 27-28.

10 For study 205, the night 2 result refers to a mean of nights 1-2, and the night 5 result refers to a mean of nights 4-5.

11 For study 207, the night 2 result refers to a mean of nights 1-2.

Table 3
Efficacy Results for Zaleplon vs Placebo
Summary of Effect Sizes[1] for Trials Comparing Zaleplon and Placebo, with a Focus on Observed Cases (OC)[2] analyses of Time to Sleep Onset (TSO) or Latency to Persistent Sleep (LPS)

Study Number/Dose Group	Study Night[3] Effect Size in Minutes						
	1	2	5	7	14	21	28
201: 10 mg		15					
202: 20 mg		17					
203: 10 mg		6			4		
204: 10 mg		7			8		2
204:20 mg		13			8		0
205: 10 mg		11					
205: 20 mg		17	7				
207: 5 mg		7	7				
207: 10 mg		16					
209: 10 mg	3						
210: 10 mg	7						
301: 10 mg				17	13	9	12
301: 20 mg				22	18	15	17
303: 10 mg				14	15	11	8
303: 20 mg				17	16	13	9
306: 5 mg				-5	17		
306: 10 mg				16	25		
307: 10 mg				9	15		
307: 20 mg					16		
308: 5 mg				17	10		
308: 10 mg				20	13		

1 Effect size was estimated by the difference between each zaleplon dose group and placebo in either raw mean LPS or TSO at the specified time point. [Note: By statistical plan, there was no correction for baseline values.]

2 Only observed cases (OC) results are provided; last-observation-carried-forward (LOCF) results were almost always comparable.

3 The assessments were based on either polysomnographic recordings in sleep lab studies (LPS) or on patient diaries completed on the mornings after dosing (TSO) for outpatient studies.

REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA #:	20-859
Sponsor:	Wyeth Ayerst
Clock Date:	December 31, 1997

Drug Name

Generic Name:	Zaleplon
Trade Name:	Sonata

Drug Categorization

Pharmacological Class:	Pyrazolopyrimidine
Proposed Indication:	Treatment of insomnia (hypnotic)
NDA Classification:	1 S
Dosage Forms:	5 and 10 mg capsules
Route:	Oral

Reviewer Information

Clinical Reviewer:	Paul J. Andreason, M.D.
Completion Date:	July 14, 1998

Table of Contents for Clinical Review of NDA 20-859

1.0 Materials utilized in review of NDA 20-859

1.1 Materials from NDA/IND

NDA 20-859 was submitted in two formats. The NDA was submitted as a paper "hard copy" that included all parts of the NDA (e.g. case report forms [CRF], case report tabulations, and case summaries) and an electronic format which included all of the NDA except the CRFs. Addendum submissions that either answered reviewer's questions or clarifying review issues were submitted in hard copy only.

The documents to which this reviewer most frequently referred were as follows:

Integrated summary of efficacy (volume 1.341)
Integrated summary of safety (volume 1.342)
Study reports for studies 301, 303, 306, 307, 308, 209, 210, 203, 204, and 205.
Cross reference master list of safety information (electronic format- volume 1.343, page 166; this was the hyper linked index to all of the individual patients summaries for patients with deaths, serious adverse events, dropouts due to adverse events, potentially clinically significant laboratory values, vital signs and ECGs)

Case report forms for the following subjects were reviewed and audited to verify reporting consistency with the patient summaries that were presented in electronic format:

11-207-2	30643-5510	30643-5608
30707-0004	30711-0011	30711-0074
30715-0005	30721-0008	30725-0026
30716-0046		

1.2 Related reviews and consults for the NDA

Animal toxicology shall be reviewed by Aisir Atrakchi, Ph.D.. Pharmacokinetics and metabolic studies shall be reviewed by Ruihua Yuan, Ph.D.. Chemistry shall be reviewed by Richard T. Lostritto, Ph.D.. These reviews are pending at the time of this report.

1.3 Other resources

None

2.0 Background

2.1 Indication

Zaleplon has been developed for the treatment of insomnia. The sponsor argues that zaleplon represents a safe alternative to

benzodiazepines, which can present significant troublesome side effects, including the possibility of tolerance after repeated use, and the potential for withdrawal symptoms. The sponsor also argues that zaleplon presents advantages over existing hypnotics by its absence of significant effects on memory and minimal rebound insomnia.

2.2 Administrative history

The initial IND [redacted] An end of phase II meeting was held on November 17, 1995 where it was suggested that the sponsor explore other treatments of insomnia than chronic primary insomnia. It was also suggested that patients in phase III studies not be excluded for histories of hepatitis unless the sponsor wished to contraindicate the drug in this patient population. The sponsor subsequently allowed patients with histories of hepatitis to enroll in phase III studies. A pre-NDA meeting was held with the sponsor on May 7 1997 where the sponsor proposed a computer assisted NDA format.

2.3 Proposed labeling

The dosing instructions in the draft labeling suggest zaleplon 10 mg at bed time for the treatment of insomnia for adults under the age of 65 years. The sponsor suggests that patients aged 65 years or older be started and 5 mg at bedtime.

2.4 Foreign marketing

Zaleplon is yet to be marketed anywhere in the world.

3.0 Chemistry, manufacturing, and controls

The chemical name for zaleplon is N-[3-(3- Cyanopyrazolo[1,5-a] pyrimidin- 7- yl) phenyl] -N- ethylacetamide.

The molecular formula for zaleplon is $C_{17}H_{15}N_5O$

The molecular weight of zaleplon is 305.33.

Zaleplon was found to be very stable in the solid state. No appreciable degradation was detected after storage of the drug substance for 48 months at 23 ° C, 4 months at 42° C, and 2 months at 56° C.

4.0 Animal pharmacology and toxicology

The toxicity of zaleplon was evaluated in acute oral (PO), intravenous (IV), and intraperitoneal (IP) studies in mice and rats; in a 2- week repeated- dose PO study in mice, in 2-¬ week repeated- dose IV studies in rats and dogs, and repeated- dose PO studies in rats and dogs for up to 1 year. The carcinogenic potential of zaleplon was evaluated in mice and rats. Special

toxicity studies assessing atropine interaction and effects on the endocrine system in rats, dermal and ocular irritation in rabbits, and in vitro human blood compatibility were conducted. Zaleplon was evaluated in a fertility and general reproductive performance study in rats, developmental toxicity studies in rats and rabbits, and a perinatal and postnatal development study in rats. Specific reproductive endpoints were evaluated further in rat male and female fertility studies and in a rat perinatal and postnatal cross- fostering study. The mutagenic potential of zaleplon was evaluated in a battery of in vitro and in vivo assays. Additional toxicity studies were conducted with the metabolites, M2 (primary human metabolite) and M1, which are not pharmacologically active. Zaleplon's ability to induce the cytochrome P_{450} system was assessed in mice and rats. Single-dose studies and repeated- dose studies for up to 1 year were conducted to characterize the toxicokinetics of zaleplon in mice, rats, and dogs.

Animal models of sedation suggested that zaleplon was as effective at producing sedation as other approved hypnotic agents.

Carcinogenicity and mutagenicity studies were performed and zaleplon was found to be neither mutagenic nor carcinogenic.

CNS depression was observed at all doses tested (3 mg/kg/day in rats and 5 mg/kg/day in dogs). This is an exaggeration of the pharmacologic effect. Convulsions in rats and dogs were seen at dosages of 20 mg/ kg/ day, and are known to occur with other compounds that bind to benzodiazepine receptors (lorazepam, estazolam, quazepam, diazepam, alprazolam, flurazepam, triazolam) and are considered to be a symptom of pharmacological withdrawal between daily gavage doses. Increased mortality occurred in the 1- year studies at dosages of 5 mg/ kg/ day in rats and of 20 mg/ kg/ day in dogs. In dogs, there was a clear relationship between withdrawal convulsions and death. In rats, while this relationship was not clearly evident on the day of death, withdrawal convulsions at 20 mg/ kg/ day and CNS depression at all doses were considered to be the contributing factors leading to mortality. There was no evidence of cardiovascular dysfunction or histopathology findings in the brain to account for the increased mortality and/ or convulsions.