SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Sonata. This scientific discussion has been updated until 1 September 2003. For information on changes after this date please refer to module 8B.

1. Introduction

Zaleplon is a new chemical entity, a pyrazolopyrimidine hypnotic structurally different from currently authorised benzodiazepines. The proposed therapeutic indication is "for the treatment of patients with insomnia who have difficulty falling asleep. It is indicated only when the disorder is severe, disabling or subjecting the individual to extreme distress" It is not yet authorised in any country. The dossier presented was considered to be of good overall quality, and the development has been conducted in accordance with the relevant CPMP guideline.

2. Chemical, pharmaceutical, and biological aspects

Composition

Zaleplon is presented as 5 mg and 10 mg capsules, containing a new active ingredient, zaleplon. As the drug substance is only very slightly soluble in water, it is micronised to give a consistent particle size. Other ingredients include microcrystalline cellulose; pregelatinised starch, silicon dioxide, sodium lauryl sulphate, magnesium stearate, lactose monohydrate, indigo carmine (E132) and titanium dioxide (E171) are standard. The opaque capsule shell is composed of gelatin and titanium dioxide, contains sodium lauryl sulphate and silicon dioxide and is printed using pink ink for the 10mg strength and a gold ink for the 5mg strength. The opaque light brown capsule of the 5mg capsule also contains red, yellow, and black iron oxides (E172).

Due to CPMP concerns about the possibility of covert administration of the product to others, the originally proposed formulation has been revised to include an intense blue colorant (indigo carmine) and an opacifier (titanium dioxide). The latter initially forms a noticeable film on the surface of liquids, disperses readily and makes a clear drink opaque, so those beverages, which are hard to colour, may still show evidence of tampering from the opacifier.

Manufacturing process

Ayerst-Wyeth Pharmaceutical Inc. in Guayama, Puerto Rico, manufactures the capsule formulations; a site inspection by the UK authorities in January 1997 found it to be satisfactory. The manufacturing process is simple; process optimisation and validation studies have been carried out and the results were considered satisfactory. In April 1999, the name of the manufacturer was changed to Wyeth Pharmaceuticals Company (WPC).

Control on starting materials

The applicant agreed to re-consider the limits for impurities in the active substance as further experience is gained with future batches manufactured using the current process. The proposed specification for the active substance was considered acceptable, as each of the known impurities has been qualified in toxicology studies. Zambon Group SpA manufactures Zaleplon and a Drug Master File has been submitted. Control of excipients was considered satisfactory.

Control on finished product

The finished product specification was considered acceptable once a number of modifications proposed by the CPMP were implemented. The limit for total degradation products was tightened and a commitment received from the applicant to review the limit once 36-month stability data became available. The applicant also committed to develop a second method for identity testing of zalepon in the capsule formulation. The applicant further agreed to introduce the Ph. Eur. test for uniformity of weight to tighten the dissolution specification and to limit the dissolution acceptance criteria to stage 2

for both release and end-of-shelf life. The analytical methods have been well validated. Batch analytical data comply with the specification.

Stability

Zaleplon drug substance shows good stability and supports the proposed storage period of 12 months for the active substance. The stability profile of both strengths of capsules remains good for up to 24 months with all the results within specification at 25C/60% RH. There is little evidence of degradation. All impurities except one remained below the level of 0.1%. Dissolution results remained high after 24 months storage. These results were considered sufficient to support a shelf life of two years for the capsules when stored below 30^{o}C in opaque blister packs. In September 2001, the shelf life was extended from 2 years to 3 years as foreseen at the time of the authorisation.

The applicant provided sufficient data to demonstrate that the additional excipients (indigo carmine and titanium dioxide) had no adverse effect on the quality of the product. Compatibility studies on the active and unmarked formulation blends with the two new excipients did not show any problems. Batch analytical results and preliminary stability data on the new formulation have been reviewed and considered sufficient to allow approval. The applicant has committed to supply regular updates on the stability testing of the new formulation at specific intervals.

3. Toxico-pharmacological aspects

Pharmacodynamics

Primary pharmacology: Zaleplon is a novel pyrazolopyrimidine hypnotic agent that binds weakly but specifically to the cerebral $GABA_A$ benzodiazepine (BDZ) receptor complex. The IC_{50} for displacement of (3H)-flunitrazepam in rat cortical tissue, an inverse measure of its affinity for BDZ receptors was 200nM (400-fold that of triazolam, 2-fold that of flurazepam and 50-fold that of diazepam). In addition zaleplon enhancement of GABA-induced TBPS binding (IC_{50} = 200nM, I_{max} = 73%) was similar in magnitude to the enhancement by triazolam, flurazepam and diazepam (IC_{50} = 0.5, 114, 17nM, I_{max} = 78, 71, 65% respectively). Zaleplon showed selectivity for the BZ1 or alpha 1 receptor subunit of the $GABA_A$ complex. Based on these data a fast receptor off rate and an improved therapeutic ratio for zaleplon has been postulated.

Zaleplon was active in several behavioural studies in rats and monkeys. Zaleplon, triazolam and flurazepam showed anxiolytic activity as measured by anti-conflict effects in both rats (ED_{50} = 1.1,0.4 and 3.2 mg/kg respectively) and squirrel monkeys. Zalepon, triazolam and flurazapam induced EEG changes in monkeys and rats compatible with reduced time to sleep and increased sleep time.

Studies were conducted to assess tolerance and the dependence/addiction potential of zaleplon compared with triazolam and zolpidem in rats and baboons. Moderate withdrawal symptoms (tremor, retching) were seen after two weeks and increased in severity with time. Results also indicated that zaleplon is slightly less likely to induce tolerance and as likely to induce dependence/addiction as the comparators tested.

General pharmacodynamics: Zaleplon produced a similar inhibition of activity, pain and writhing response and fall in temperature in mice and rats as compared to triazolam, flurazepam, zolpidem, pentobarbitone, and phenobarbitone. Zalepon had no effect on charcoal meal transit times in mice or acetylcholine, histamine or barium induced contractions in isolated guinea pig ileum. Zaleplon induced no adverse vasomotor or respiratory effects in rabbits. Respiratory rates and tidal volume were reduced following administration of high doses of zaleplon to monkeys breathing air or CO_2 enriched air indicating a potential muscle relaxant effect. Heart rate and blood pressure fell in both normotensive, conscious rats and spontaneously hypertensive rats. Zaleplon reduced urinary volume and Na^+ and Cl^- concentrations in rats. No effect was recorded on *in vitro* human renin activity.

Drug interactions: Studies of potential interaction with ethanol and next day residual effect showed that although zaleplon was approximately equipotent to triazolam in sedation, triazolam was considerably more active in potentiating the impairing effects of ethanol.

Pharmacokinetics

Absorption: Zaleplon is rapidly and completely absorbed in all species tested (mice, rats, dogs and monkeys).

Distribution: Zaleplon is rapidly distributed to all tissues but primarily the liver, kidney, gastrointestinal tract (GIT), adrenal glands and pancreas of rats. Passage of the blood-brain barrier appears to be limited. Studies in pregnant and lactating rats indicate slightly lower exposure in the foetus than the dam; zaleplon concentrates 3-fold in milk compared to plasma. Plasma protein binding is 50%, 34%, 44% and 60% in the mouse rat dog and man respectively.

Metabolism: Zaleplon is metabolised mainly in the liver with involvement of CYP 3A4 enzymes, although the main catalyst for 5-oxo-zaleplon formation in man is thought to be aldehyde oxidase. The main metabolites have been studied and found to be without pharmacological or toxicological activity. They are present in the animal species used in pivotal studies, although in different proportions to man.

Elimination: Excretion studies showed a high recovery in rat and dog with recovery of radiolabelled dose as metabolites rather than parent compound. Biliary excretion appears to predominate.

Repeat Administration: Studies in rats and dogs showed that steady state is reached rapidly with little or no accumulation and exposure being the same on day 1 and day 14.

Toxicology

Single dose toxicity

Studies were conducted in the mouse, rat and dog at doses up to 1000 mg/kg p.o. All adverse events were either pharmacological in origin or occurred only at extremely high doses. Given the proposed indication and dosage in man no acute toxic events are anticipated.

Repeated dose toxicity

Repeated dose studies were conducted in the mouse, rat and dog with one year studies in the rat (0-50 mg/kg/day p.o. and the dog 0-40 mg/kg/day p.o.). CNS and GIT effects were noted in all studies as before, increasing in severity with time and dose. Most adverse events were similar to the single dose studies and were either pharmacological in origin or occurred only at extremely high doses. There was a good recovery from these effects in a four-week withdrawal period.

An additional finding in the three-month study was of testicular and prostate atrophy. Zaleplon induced irreversible changes in the male reproductive system in beagle dogs after three months e.g. decrease in prostate weight, degeneration of spermatogenic epithelium, atrophy of seminiferous tubules, decrease in number of sperm. In response to a request to discuss the relevance of these finding to human treatment the applicant proposed that full recovery was thought to be possible since there were no pathological changes in spermatogonia, spermatocytes or Sertoli cells and that the study recovery period (4 weeks) encompasses only 2 cycles of the seminiferous epithelium and only half of the duration of spermatogenesis. It was also proposed that the test animals were pre-pubescent at the start of dosing and that the observed changes were consistent with delayed onset of maturity. The applicant considered that the evidence of studies in more mature dogs supported this hypothesis for similar time periods where no adverse effects on the reproductive organs were observed. The CPMP considered that a specific reference to these findings should be included in the preclinical safety data section of the SPC.

Reproductive toxicity

Adverse effects were noted on fertility and foetal development following zaleplon administration but only at toxic doses.

Genotoxicity

Zaleplon is positive at doses over 550µg/ml in the CHO chromosome aberration assay in the presence of S9 fraction, but negative in all other *in vitro* and *in vivo* genotoxicity tests, including a human lymphocyte chromosome aberration assay. The balance of evidence was considered to suggest that zaleplon is non-genotoxic.

Carcinogenicity

Carcinogenicity studies were carried out in both mice and rats. There was no increase in tumour burden compared to the controls and no carcinogenic risk is anticipated given the proposed indication in man.

Local tolerance

No adverse effects were noted following primary skin irritation and eye irritation assays in rabbits.

Environmental risk

An environmental risk assessment was carried out based on anticipated use of zaleplon throughout Europe over a five-year period. No adverse effects are anticipated.

Overall assessment toxico-pharmacological aspects

Zaleplon has been subjected to an exhaustive series of pre-clinical studies. Zaleplon is, *in vitro* and *in vivo*, a $GABA_A$ receptor agonist, similar to the benzodiazepines, whose activity is inhibited by the $GABA_A$ antagonists, e.g. flumazenil. Zaleplon is metabolised by the liver and subject to biliary excretion. The main metabolites have been studied and found to be without pharmacological or toxicological activity, they are present in the animal species used in pivotal studies, although in different proportions to man. There is no significant target organ toxicity. Zaleplon is positive in the CHO chromosome aberration assay, but negative in all other *in vitro* and *in vivo* genotoxicity tests, including a human lymphocyte chromosome aberration assay, and in carcinogenicity studies.

4. Clinical aspects

Clinical Pharmacology

***Pharmacodynamics*:** The secondary pharmacodynamic actions of zaleplon have been studied in 19 clinical trials (18 Phase I and one phase II) designed to characterise the effects on psychomotor and cognitive function, memory and learning ability, EEG, drug interaction influences on pharmacodynamic measures. These studies concentrated on the potential adverse effects of a hypnotic/anxiolytic agent i.e. on motor co-ordination, memory and mental function, respiratory depression and abuse potential.

Effects on mental and psychomotor function: In studies in which the effects of zaleplon on psychomotor performance and cognitive function were evaluated no significant impairment of psychomotor, cognitive or memory tests was observed at dose levelsup to 10 mg, either at the time of peak activity or at any subsequent time points. In studies that were designed to evaluate the effects of zaleplon on memory, results showed that zaleplon primarily affected the semantic/explicit memory and had some effects on working memory. The memory effects paralleled the effects on psychomotor performance both in terms of dose relationship and time course. At the 10-mg dose level zaleplon had little measurable effect on memory whilst at 20 mg definite impairment of explicit memory was observed. In an integrated analysis performed on data from selected tests for memory function in 11 studies the frequency of memory impairment for 20 mg of zaleplon was comparable with that observed for 10 mg zolpidem, 2 mg lorazepam or 7.5 mg zopiclone.

Residual effects on cognitive function: A 6-period cross-over study (04) compared the effects on learning and mental function of zaleplon 10 mg, 20 mg, zolpidem 10 mg, 20 mg triazolam 0.25 mg and placebo. Subjects were woken 1.25 and 8.25 hr later and a battery of tests were administered. Immediate and delayed word recall was impaired compared to placebo in a dose response manner and with the order of increasing impairment zaleplon 10 mg < zaleplon 20 mg = triazolam 0.25 mg= zolpidem 10 mg < zolpidem 20 mg.

Next day sedation (hang-over effect) was assessed (05) in healthy volunteers after 10 or 20 mg zaleplon, 30 mg flurazepam or placebo. MSLT times for both zaleplon groups was slightly though non-significantly shorter than that for the placebo group whereas MSLT times were significantly shorter for the flurazepam group. A similar study (14) in patients with sleep maintenance insomnia showed that sleep latency was 15 minutes after placebo, 17 minutes after zaleplon 10 mg and 5 minutes after flurazepam 30 mg (a statistically significant shortening for the latter).

Effects on respiratory function: In a study in patients with insomnia and mild to moderate chronic obstructive disease (FEV_1 35-80% predicted normal) single doses of zaleplon 10 mg or zolpidem 10 mg did not lead to clinically important changes in oxygen saturation. Similarly in patients with obstructive or mixed sleep apnoea results were very similar to placebo. Nevertheless, sleep apnoea remains a contraindication to the use of zaleplon as per the CPMP guideline (see section 4.2 SPC, *Posology and method of administration*).

Anxiety: Several studies examined the possible occurrence of daytime anxiety and anxiety associated with discontinuation of treatment. The results showed that administration of zaleplon doses of 5, 10, 20mg for up to 29 days did not result in daytime anxiety or anxiety associated with discontinuation of treatment.

Pharmacokinetics

The pharmacokinetics of zaleplon have been investigated in 30 studies involving a total of more than 500 healthy subjects (young and elderly), nursing mothers, and patients with renal or hepatic disease. In healthy subjects the pharmacokinetic profile has been examined after single doses up to 60 mg and multiple doses up to 30 mg, administered daily for up to 10 days.

Absorption: Zaleplon is rapidly and almost completely absorbed after oral administration with T_{max} in the region of 1 hour. However, because zaleplon undergoes significant pre-systemic metabolism, its absolute bioavailability is approximately 30%. Dose linearity of plasma pharmacokinetics has been confirmed in two studies. Food prolonged the absorption of zaleplon thereby delaying T_{max} by approximately 2 hrs (1.4 to 3.7hrs) and reducing C_{max} by approximately 35%. AUC and $t_{1/2}$ were not affected. To maintain rapid sleep onset, administration of zaleplon with or immediately after food is not recommended.

Distribution: Zaleplon is a lipophilic compound with a volume of distribution of ~ 1.3 l/kg at steady state including substantial distribution into extravascular tissues. The *in vitro* plasma protein binding for zaleplon is ~ 60% (~77% for the N-desmethyl metabolite) and is not concentration-dependent. The blood to plasma ratio for zaleplon is ~ 1. Zaleplon is present in human milk with a plasma milk ratio of ~ 0.5 and zaleplon is not recommended for use in nursing mothers.

Metabolism: After oral administration zaleplon is extensively metabolised with less than 1% of the dose excreted unchanged in the urine. Metabolism is primarily by the aldehyde-oxidase to form 5-oxo-zaleplon, which accounts for 22% and its glucuronide, which accounts for an additional 35% of drug related substance. Zaleplon is also metabolised to a lesser extent by CYP3A4 to from desethyl-zaleplon, which is quickly transformed to 5-oxo-desethyl-zaleplon before glucuronidation. It is probable, on the basis of animal studies that the metabolites are pharmacologically inactive but this assumption has not been tested in man.

Elimination: After both oral and iv administration zaleplon is rapidly eliminated with a mean half-life of ~1 hr. Approximately 88% of radiolabelled drug was recovered within 5 days, 71% in the urine and 17% in the faeces. The urinary recovery of drug related substance was as 5-oxo-zaleplon (~22%) its glucuronide metabolite (~35%), 5-oxo-desethylzaleplon (~6%) and its glucuronide metabolite (~3%) with other unidentified minor metabolites (~4%). No unchanged zaleplon or desethyl-zaleplon was recovered in the urine.

Special Populations

The Elderly: In two studies comparing elderly to young subjects, the pharmacokinetic profile of zaleplon in elderly subjects was not significantly different from those in young subjects. In the study with elderly subjects 65-75 yrs, C_{max} and AUC were 11% and 8% lower whereas in the study with elderly subjects aged 75 yrs and over C_{max} and AUC were 12% and 28% higher as compared with the young subjects. Despite these results a reduction in the starting dose is proposed for the elderly in view of their generally recognised greater sensitivity to sedative and hypnotic agents.

Hepatic Impairment: A study was conducted in subjects with biopsy-proven hepatic cirrhosis and healthy controls and showed that with decreasing hepatic function there is reduced metabolism and clearance of zaleplon with consequential greater exposure. Zaleplon is contraindicated patients with severe hepatic insufficiency and a lower starting dose (5 mg) is indicated with mild to moderate hepatic impairment.

***Renal Impairment*:** The plasma concentrations of zaleplon were not significantly different in patients with varying degrees of renal insufficiency as renal excretion of unchanged zaleplon accounts for less than 1% of the administered dose. No specific dosage adjustment is required in patients with renal insufficiency.

Drug Interactions

Zaleplon was evaluated in healthy volunteers for drug-drug interactions with CNS active drugs (ethanol, imipramine, thioridazine and paroxetine), drugs that are likely to alter the biotransformation of zaleplon by enzyme induction (rifampicin) or inhibition (cimetidine and diphenhydramine) and drugs that are likely to affect renal excretion (ibuprofen). Likewise, the effects of zaleplon on drugs that are likely to be taken concomitantly was also investigated.

***CNS active drugs*:** The interaction of ethanol (0.75 mg/kg) and zaleplon 10 mg, triazolam 0.25 mg with and without ethanol as a control was measured in healthy subjects. Complex reaction times were increased 2% in the presence of ethanol, 11% in presence of zaleplon, 94% with triazolam and 27% for zaleplon and ethanol.

In order to assess the sedative effects of zaleplon and imipramine taken in combination, healthy subjects were given a single 75-mg dose of imipramine concomitantly with a single 20-mg oral dose of zaleplon. Three psychomotor tests showed an interaction, which was additive for two tests and more that additive for one. The interaction was entirely pharmacodynamic with no alteration of the pharmacokinetic profile of the drug.

In studies with thioridazine an additive effect was observed on two psychomotor tests, which was purely pharmacodynamic with no alteration of the pharmacokinetic profile of either drug.

Similarly, paroxetine did not significantly affect the pharmacodynamic or pharmacokinetic profile of zaleplon.

In 2002, section 4.5 of the SPC was updated following a multiple dose study between zaleplon and venlafaxine (extended release) with the information that no interaction on psychomotor performance or pharmacokinetic parameters was observed.

***Enzyme Inducers/Inhibitors*:** Rifampicin 600 mg was given to healthy volunteers for 14 days. Zaleplon C_{max} and AUC were four-fold lower compared to baseline suggesting induction of hepatic and intestinal metabolism. Although oxidation by CYP3A4 is a minor metabolising pathway for zaleplon these results indicated that co-administration of CYP3A4 inducers although not posing a safety concern would reduce the hypnotic effect of zalpelon.

Cimetidine is unique in that it has the potential to inhibit both aldehyde oxidase and CPY3A4. Co-administration of cimetidine 800 mg increased the mean C_{max} and AUC of zaleplon by 85% associated with a 44% decrease in oral dose clearance and significant change in $t_{1/2}$ terminal. However based on the safety profile for zaleplon and its short half-life, adjustment of the 10 mg therapeutic dose should not be necessary. A caution was also introduced to the SPC regarding the concomitant use of strong selective CYP3A4 inhibitors such as ketoconazole or erythromycin.

In 2000, the MAH demonstrated that co-administration of zaleplon and erythromycin, a strong selective CYP3A4 inhibitor, results in a mean increase of approximately one third in the Cmax and one fifth in AUC of zaleplon. No safety concern was envisaged given that zaleplon seems well tolerated, and has an elimination half-life of approximately one hour. Therefore, a routine dosage adjustment of Sonata is not considered necessary, but patients should be advised that the sedative effects might be enhanced. In December 2000, information was included in section 4.5 of the SPC that patients should be advised that the sedative effects might be enhanced.

There was no pharmacokinetic interaction between zaleplon (10 mg) and diphenhydramine (50 mg) after single dose administration. Because both of these compounds have a sedative/hypnotic effect, co-administration should be approached with caution.

***Drugs affecting renal excretion*:** There was no apparent pharmacokinetic interaction in studies with ibuprofen.

***Drugs with a narrow therapeutic index*:** There was no apparent pharmacokinetic interaction in studies with digoxin.

The potential for drug interaction between warfarin (25 mg days 1-13) and zaleplon (20 mg days 6-17) was studied over a 17-day period. The mean AUC of the prothrombin time expressed as the international normalised ratio (INR) was ~5% less than for warfarin treatment alone.

Clinical experience

The applicant has conducted a series of 14 Phase II and III studies, five of which have non-blinded long term safety extensions. The studies are of excellent overall quality and have been conducted using methods, which change very little from trial to trial, and are described briefly below.

Inclusion/exclusion criteria: The great majority of patients studied had primary insomnia, or insomnia associated with mild non-psychotic psychiatric disorders, as defined by the American Psychiatric Association DSM-III-R criteria. In addition to satisfying the diagnostic criteria patients should experience symptoms of daytime impairment attributable to the sleep disturbance; typical time to sleep onset of $\geq$ 30 minutes; prolonged or frequent nocturnal awakenings, or total sleep time of $\leq$ 6 ½ hours on average.

The list of exclusion criteria for the Phase III studies runs to 19 items designed to exclude patients with secondary insomnia, sleep apnoea syndrome and other non-related serious illness or drug abuse.

Efficacy criteria: The Phase II clinical trials were sleep clinic studies using polysomnography (PSG) to record Latency to Persistent Sleep (LPS); Total Sleep Time (TST); Number of Awakenings After Sleep Onset (NAASO); and Sleep Architecture. The primary outcome in Phase III studies was questionnaire-elicited change in reported time to sleep onset (TSO). This is a commonly used variable and directly assesses the primary sleep complaint of difficulty falling asleep; a wide range of other variables were also assessed and evaluated as secondary criteria.

Statistical methods: Data handling and statistical analyses followed standard practice and relevant CPMP guidelines. Efficacy variables were analysed for the intent-to-treat population (those who received any trial medication) and for the efficacy-evaluable population (those receiving trial medication and having no major protocol violations). Secondary analyses included last observation carried forward for drop-outs and the efficacy evaluable population. Inference testing was by Dunnett's Test, which is intended for comparing a number of treatments with a single control, and the Jonckheere-Terpstra test for detecting departures from independence in a contingency table.

Results: The organisation of the phase II and II studies are indicated in Table 1. Table 2 provides a summary of the TSO comparisons with placebo in outpatient and sleep laboratory studies and Table 3 provides a summary of the TTS comparisons in the same studies.

Phase II Dose ranging studies: Study 12 can be taken as representative of several clinical trials aimed at defining the optimal dose. It was a 5-night parallel group trial of zaleplon 2, 5, 10 and 20 mg and placebo in patients with primary insomnia. Twenty-seven to twenty-eight patients completed the study in each dosage group. Sleep latency was significantly decreased for patients receiving zaleplon 10 mg and 20 mg but not for 2 mg and 5 mg, which with the exception of elderly patients seems too low a dose. Phase III studies have also been conducted with dose response and dose definition in mind and indicate that 10 mg seems an appropriate usual dose.

Table 1 ORGANIZATIONAL GROUPINGS OF STUDIES

Placebo-Controlled Studies

Outpatient Studies	**Sleep Laboratory Studies**	
Chronic Insomnia Patients	Chronic Insomnia Patients	Transient Insomnia Models
Nonelderly	*Nonelderly*	*Nonelderly*
17 28-day parallel (5, 10, 20 mg)[a] [10 mg zolpidem]	08 (Dose Ranging) 2-day crossover (10, 40 mg) [0.25 triazolam]	15 Phase advance crossover (5, 10 mg) [7.5 mg zopiclone]
19 28-day parallel (5, 10, 20 mg) [10 mg zolpidem]	09 (Dose Ranging) 2-day crossover (20, 60 mg) [0.25 triazolam]	16 First night effect (5, 10 mg)
22 14-day parallel (10, 20 mg)	10 14-day parallel (5, 10 mg) [0.25 mg triazolam]	
	11 28-day parallel (10, 20 mg) [10 mg zolpidem]	
	12 5-day parallel (2, 5, 10, 20 mg)	
Elderly	*Elderly*	
21 14-day parallel (5, 10 mg) [5 mg zolpidem]	13 2-day crossover (2, 5, 10 mg)	
23 14-day parallel (5, 10 mg)		

Uncontrolled Outpatient Studies (up to 12 months)

Nonelderly	*Elderly*
18 Open-label 17 extension, ongoing (10 mg)	21 Open-label 21 extension, ongoing (5, 10 mg)
20 Open-label 19 extension, completed (10 mg)	23 Open-label 23 6 months extension, ongoing (5, 10 mg)
24 Open-label 22 extension, ongoing (10, 20 mg)	

a: The doses in parentheses are the zaleplon doses given in the study.

TABLE 2. SUMMARY TSO--COMPARISONS WITH PLACEBO[a] IN OUTPATIENT AND SLEEP LABORATORY STUDIES

Study Period	Protocol 0897A1-	Zaleplon 2 mg[b]	Zaleplon 5 mg[b]	Zaleplon 10 mg[b]	Zaleplon 20 mg[b]	Triazolam 0.25 mg[c]	Zolpidem 5 mg[c]	Zolpidem 10 mg[c]
Outpatient								
Week 1	17	-	0.044	0.002	<0.001	-	-	0.008
	19	-	0.014	0.001	<0.001	-	-	0.047
	22	-	-	<0.001	-	-	-	-
	21[d]	-	*ns*	*<0.001*	-	-	*0.021*	-
	23	-	*0.001*	*< 0.001*	-	-	-	
Week 2	17	-	ns	ns	<0.001	-	-	ns
	19	-	0.006	0.003	<0.001	-	-	0.006
	22	-	-	<0.001	<0.001	-	-	-
	21	-	*<0.001*	*<0.001*	-	-	*0.004*	-
	23	-	*< 0.001*	*<0.001*	-	-		-
Week 3	17	-	ns	0.014	<0.001	-	-	ns
	19	-	0.010	0.010	<0.001	-	-	0.043
Week 4	17	-	ns	ns	<0.001	-	-	0.033
	19	-	ns	0.028	0.006	-	-	ns
Sleep laboratory								
Nights 1-2	10	-	ns	0.003	-	0.015	-	-
	11	-	-	ns	0.006	-	-	0.006
	12	ns	ns	ns	0.005	-	-	-
	13[e]	*ns*	*0.043*	*<0.001*	-	-	-	-
Nights 4-5	12	ns	0.017	<0.001	<0.001	-	-	-
Nights 13-14	10	-	ns	ns	-	ns	-	-
	11	-	-	<0.001	0.006	-	-	<0.001
Nights 27-28	11	-	-	ns	ns	-	-	ns

a: P-values indicate significantly different from placebo, "ns" indicates not significantly different from placebo, "-" indicates that the dose was not given in that study.

b: From Dunnett's test, which adjusts by the number of zaleplon treatments in the study.

c: From unadjusted pairwise comparisons.

d: Studies in elderly patients are indicated by italics.

e: Study 13 was a crossover study.

TABLE3. SUMMARY TTS--COMPARISONS WITH PLACEBO[a] IN OUTPATIENT AND SLEEP LABORATORY STUDIES

Study Period	Protocol 0897A1-	Zaleplon 2 mg[b]	Zaleplon 5 mg[b]	Zaleplon 10 mg[b]	Zaleplon 20 mg[b]	Triazolam 0.25 mg[c]	Zolpidem 5 mg[c]	Zolpidem 10 mg[c]
Outpatient								
Week 1	17	-	ns	ns	0.011	-	-	<0.001
	19	-	ns	ns	0.026	-	-	<0.001
	22	-	-	0.006	-	-	-	-
	21[d]	-	*ns*	*0.024*	-	-	*<0.001*	-
	23	-	*ns*	*0.042*	-	-	-	
Week 2	17	-	ns	ns	ns	-	-	0.013
	19	-	ns	ns	0.029	-	-	<0.001
	22	-	-	0.009	0.001	-		-
	21	-	*ns*	*ns*	-	-	*0.010*	-
	23	-	*ns*	*ns*	-	-	-	-
Week 3	17	-	ns	ns	0.047		-	0.003
	19	-	ns	ns	ns	-	-	<0.001
Week 4	17	-	ns	ns	ns	-	-	0.009
	19	-	ns	ns	0.044	-	-	<0.001
Sleep laboratory								
Nights 1-2	10	-	ns	ns	-	0.049	-	-
	11	-	-	ns	ns	-	-	ns
	12	ns	0.050	ns	ns	-	-	-
	13[e]	*ns*	*ns*	*0.028*	-	-	-	-
Nights 4-5	12	ns	0.032	ns	ns	-	-	-
Nights 13-14	10	-	ns	ns	-	ns	-	-
	11	-	-	ns	ns	-	-	0.012
Nights 27-28	11	-	-	ns	ns	-	-	ns

a: P-values indicate significantly different from placebo, "ns" indicates not significantly different from placebo, "-" indicates that the dose was not given in that study.

b: From Dunnett's test, which adjusts by the number of zaleplon treatments in the study.

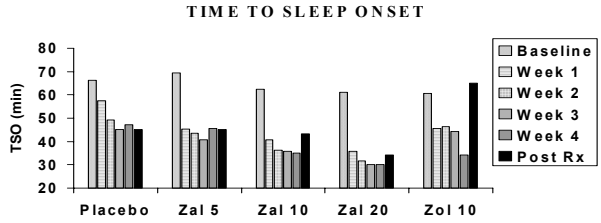
c: From unadjusted pairwise comparisons.

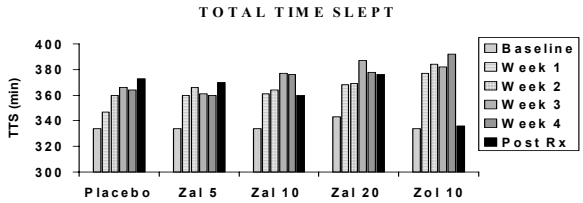
d: Studies in elderly patients are indicated by italics.

e: Study 13 was a crossover study.

Phase III studies - active comparator controlled

Study 17. Was a parallel-group dose ranging study with zolpidem 10 mg as an active comparator and placebo as a negative control? After a one-week run in (baseline) patients received zaleplon 5, 10, 20 mg for four weeks followed by one week off treatment. The principal efficacy criteria were Time to Sleep Onset (TSO) and Total Time Slept (TTS). For the zaleplon 5-mg, dose statistical significance against placebo was intermittent for TSO indicating that it is probably a sub-optimal dose. The 10 and 20-mg dose retained significance at weeks one and three. For TTS the lower two doses of zaleplon did not achieve significance against placebo, the 20-mg dose achieved intermittent significance (weeks 1 and 3). Zolpidem 10 mg was significantly better than placebo over the four treatment weeks for TTS and at weeks one and four for TSO. Zolpidem was significantly worse in the run-off period indicating a probable withdrawal effect.





Study 19 was a study of almost identical design to Study 17, described above, but conducted in Europe and Canada. One investigative centre was excluded from analysis prior to the code being broken and five others afterwards, because of poor quality of data relating to poor data recording and poor compliance with procedures on behalf of the investigators at the centres excluded. However analyses with and without those centres were concordant. For TSO with the exception of the 5-mg dose at week 4 all comparisons indicated a significant advantage for zaleplon over placebo; zolpidem had a significant advantage over placebo during weeks 1-3 but this was lost in week 4. For TTS the 5-mg dose of zaleplon had a non-significant advantage, the two higher doses of zaleplon and the single dose of zolpidem achieved statistical significance at most time points.

Study 23 was a 14-day study of 5 and 10 mg zaleplon in elderly outpatients with insomnia. Differences from placebo are statistically significant ($p < 0.001$) for TSO but not for TTS.

Study 21 was a 14-day study of 5 and 10 mg zaleplon and 5 mg of zolpidem in elderly outpatients with insomnia. For TSO the 10-mg dose of zaleplon was significantly better than placebo over the two treatment weeks ($p < 0.001$). For TTS the lower dose of zaleplon did not attain a significant difference and for the higher dose significance was lost after week one.

Overall assessment of efficacy

The applicant has demonstrated through a series of well-conducted clinical trials that zaleplon is a safe and effective hypnotic. It has advantages over comparable treatments in its rapid onset and low propensity to cause carryover effects on the following day. The 10-mg and 20-mg doses of zaleplon are effective for sleep induction in non-elderly insomniacs and this effect is maintained for 2-4 weeks. The 5-mg dose of zaleplon is similarly effective for sleep induction in elderly insomniacs. It has a disadvantage in that it did not show statistically significant differences from placebo for sleep maintenance measures. With respect to sleep continuity no advantage over placebo was shown in 3 out of 4 studies reviewed whereas with sleep duration superiority over placebo was demonstrated in 4/8 studies though in some the increase of 10 minutes was considered of limited clinical relevance. The 5-mg and 10-mg doses of zaleplon in non-elderly insomniacs do not appear to be effective for sleep maintenance. However, the 10-mg dose is efficacious in this respect for the elderly insomniacs whilst the 20 mg is effective even for the non-elderly. There was insufficient data on functions other than sleep induction in the published literature to allow worthwhile comparisons to be made between zaleplon and other short acting hypnotics e.g. zolpidem and triazolam.

In order to address the above concern the therapeutic indication (section 4.1 SPC, *Therapeutic indications*) has been modified to show that zaleplon is indicated for the treatment of patients who have difficulty falling asleep as follows:

"Zaleplon is indicated for the treatment of patients with insomnia who have difficulty falling asleep. It is indicated only when the disorder is severe, disabling or subjecting the individual to extreme distress."

and the section 4.4 of the SPC, *Special warnings and special precautions for use* has also been modified to include:

"Due to zaleplon's short plasma half-life alternative therapy should be considered if early morning awakening is experienced. Patients should be advised not to take a second dose within a single night."

In line with previous CPMP guidance with respect to the use of benzodiazepine and benzodiazepine-like agents treatment with zaleplon should be as short as possible. In the SPC the maximum duration of treatment is specified as two weeks.

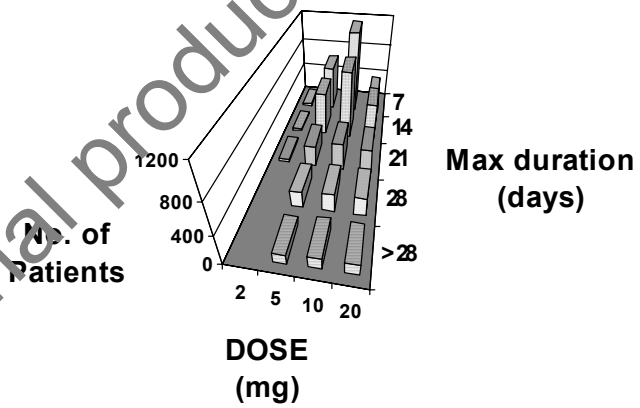
Safety

The safety database is comprised of patients exposed to treatments in clinical trials as shown in Table 4. Exposure to zaleplon by dose is illustrated below.

Table 4 Numbers of patients in clinical trials according to treatment

	Zaleplon	Active comparator	Placebo
Healthy volunteers	748	346	318
High-risk special groups	97	49	49
Phase II/III	2831	560	1028

EXPOSURE TO ZALEPLON BY DOSE AND DURATION



Abuse potential

The abuse potential of zaleplon and triazolam were compared in two clinical studies. In study **01** six subjects with a history of sedative drug misuse took ascending single doses of 0, 10, 20, 40, 60, 75 mg zaleplon and 0, 0.25, 0.5, 0.75 mg triazolam. Due to the small number of patients Addiction Research Centre data (ARCI) were not analysed and equivalence of doses was determined by psychomotor testing. The impairment in psychomotor skills increased with dose and apart from minor differences in the time course was similar between the two treatments.

In study **02** in fourteen subject's psychomotor performance was similar between the two drugs in 4/8 tests; in 1/8 performance was better after zaleplon and in 3/8 was better after triazolam. The phenobarbitone/chlorpromazine/alcohol sub-scale of ARCI was significantly different from placebo for the mid and high doses of zaleplon and for the high dose of triazolam. This study was considered not sufficiently powerful to discriminate between the two drugs and the results indicate that there is some risk of abuse for both products examined.

Concern was expressed by the CPMP regarding the potential misuse of zaleplon by covert administration to others. Zaleplon is quick acting, short-lived, is in a capsule formulation and has little taste. Thus it could be easily administered to an unknowing victim in a drink. In response to this concern the applicant reformulated the product to introduce two markers so that if the capsule is dissolved in liquid the liquid changes colour and becomes cloudy. A statement to this effect is included in the patient information leaflet.

Clinical safety

Deaths: One patient, a 57-year old man, died by suicide shortly after a clinical trial. Although it is possible that he may have had occult depression aggravated by a sedative treatment the event is unique and is more likely to be due to coincidence than cause and effect. Another patient died suddenly from an unknown cause during the placebo run-in phase.

Withdrawal from studies due to adverse events: Withdrawal from placebo-controlled clinical trials due to adverse events occurred in 3% of patients taking zaleplon 5 mg; 2% of patients taking zaleplon 10 mg and in 4% of patients on zaleplon 20 mg. The corresponding rates for active comparator treatments and placebo were 4% and 3% respectively. It was considered that there were no safety-related reasons for dropouts, which differed significantly among the various doses of zaleplon, the active comparators and placebo.

Serious adverse events: The definition of a serious adverse event used by the applicant includes one causing, but not explicitly prolonging hospitalisation, nevertheless the martial included was considered to be within the usual regulatory meaning and is shown in Table 5. It should be noted that the figures are numbers (not percentage) of patients and do not give an indication of the frequency of events.

Of particular interest are CNS events of which amnesia, depersonalisation, and paraesthesia occurred in a dose-related manner and were statistically more frequent for zaleplon 20 mg than for placebo. Hallucination and hypaesthesia were also significantly more frequent with zaleplon 20mg but with less evidence of a dose response relationship.

Five patients experienced syncopal episodes and eleven experienced other cardiovascular events, which were of a heterogeneous nature and did not occur in a dose-related manner. They are more likely to be related to the patient's age and the presence of underlying disease than to therapy.

Cancer: The applicant indicates that twelve patients in Phase II/III studies were diagnosed as having cancer while in zaleplon studies or shortly thereafter. Although the applicant did not make any assessment of causality most cancers are known to have silent growth phases of years before clinical presentation and given the short exposure to zaleplon any causal association was considered extremely unlikely.

Table 5 shows numbers of patients - by treatment - experiencing serious adverse events

	Zal 5 mg	**Zal 10 mg**	**Zal 20 mg**	**Zal > 20 mg**	**Pbo**	**Active comp**	**Other**
Body	9	17	3	0	3	0	3
CVS	10	13	4	0	7	2	7
GIT	6	2	4	0	1	0	2
Endo	0	1	0	0	0	0	0
Haematol	1	2	0	0	0	0	0
CNS	1	13	15	4	3	8	2
Resp	3	5	0	0	0	1	1
Cutan	2	2	0	0	0	1	1
Sp Sens	0	1	1	0	0	0	0
Urogen	3	11	2	0	2	0	1
Misc	2	12	1	0	5	0	0

Adverse events: In placebo-controlled trials, 6% of patients treated with zaleplon and 4% of patients treated with placebo experienced somnolence. Overall based on the results of clinical studies the most apparent undesirable effects that might be expected from zaleplon involve mild headache, asthenia, somnolence and dizziness.

Laboratory Abnormalities: In the parallel group placebo-controlled studies, 8 patients had clinically important changes in transaminase levels. One tested positive for hepatitis C and two had elevated values at screening. In the remaining 5 patients, 3 had been treated with zaleplon 5 mg, one with zolpidem 10 mg, and one with placebo. In extended open-label studies, three of the 1088 patients had increases in AST or ALT; two were hepatitis C positive: no cause was found for one patient. Sporadic increases in bilirubin levels were noted, amounting to 0.6% of patients exposed to zaleplon, 0.3% of patients treated with active comparators and 0.3% of placebo treated patients. Many of the elevations were found to pre-date exposure to treatment and no pattern was found. Abnormalities of ECG were found in 0.7% of zaleplon treated patients. No consistent pattern emerges; many of the patients were over sixty-five and had risk factors for cardiac disease. One patient is listed as discontinuing the study for abnormalities of the 'haemic and lymphatic' systems but no other details are readily available. Minor and inconsistent abnormalities of urea and electrolytes emerge but do not appear to have any relationship to treatment.

Rebound insomnia and other withdrawal effects: Rebound insomnia did not occur with the 5 and 10-mg doses of zaleplon. There was subjective evidence for the occurrence of rebound insomnia with zaleplon 20 mg, triazolam 0.25 mg and zolpidem 5 mg following abrupt discontinuation of treatment after 2 weeks of administration.

In 2002, a statement was added to section 4.4 of the SPC alerting the physician to the fact that insomnia may be secondary to underlying physical or psychiatric disorder and that insomnia that persists or worsens after a short course of zaleplon treatment may indicate a need to re-evaluate the patient. In addition, to reduce the risk of psychomotor impairment following use of benzodiazepines and benzodiazepine-like agents, patients should not undertake unexpected activities, e.g. driving where potential psychomotor impairment might be dangerous for 4 hours or more after taking Sonata. The paragraph on psychiatric and "paradoxical" reactions were updated with the information that these reactions may be drug-induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder and that any new behavioural sign or symptom requires careful and immediate evaluation.

No dosage adjustment is required in patients with mild to moderate renal insufficiency, because Sonata pharmacokinetics is not altered in such patients. In 2002, information was added to section 4.2 of the SPC that the safety in patients with severe renal impairment has not been studied.

5. Overall conclusion on the quality, safety, efficacy and benefit risk assessment

Quality

The quality of this product is considered acceptable when used in accordance with the conditions in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Pre-clinical pharmacology and toxicology

Zaleplon has been subjected to an exhaustive series of pre-clinical studies.

Zaleplon is, *in vitro* and *in vivo*, a $GABA_A$ receptor agonist, similar to the benzodiazepines, whose activity is inhibited by the $GABA_A$ antagonists, e.g. flumazenil.

Zaleplon is metabolised by the liver and subject to biliary excretion. The main metabolites have been studied and found to be without pharmacological or toxicological activity, they are present in the animal species used in pivotal studies, although in different proportions to man.

There is no significant target organ toxicity. Zaleplon is positive in the CHO chromosome aberration assay, but negative in all other *in vitro* and *in vivo* genotoxicity tests, including a human lymphocyte chromosome aberration assay, and in carcinogenicity studies.

Efficacy

The applicant has demonstrated through a series of well-conducted clinical trials that zaleplon is a safe and effective hypnotic. It has advantages over comparable treatments in its rapid onset and low propensity to cause carryover effects on the following day.

The 10-mg and 20-mg doses of zaleplon are quite effective for sleep induction in non-elderly insomniacs and this effect is maintained for 2-4 weeks. Similarly effective for sleep induction in elderly insomniacs is the 5-mg dose of zaleplon.

It has a disadvantage in that it is probably a less effective agent than others in terms of sleep maintenance. The 5-mg and 10-mg doses of zaleplon in non-elderly insomniacs do not appear to be effective for sleep maintenance. However, the 10-mg dose is efficacious in this respect for elderly insomniacs whilst the 20 mg is effective even for the non-elderly.

Results from the clinical trial development programme support approval for the use of zaleplon "for the treatment of patients with insomnia who have difficulty falling asleep". The attention of prescribers is drawn to the short half-life of zaleplon, and the need to consider alternative therapy if early morning awakening is experienced.

Safety

No major CNS or other side effects were associated with the 5 and 10-mg doses studied and there was no evidence for the occurrence of rebound insomnia or other withdrawal effects following their abrupt discontinuation. The 20-mg dose of zaleplon was however associated with a higher incidence of CNS effects amnesia, depersonalisation, hallucinations, hypoaesthesia and paraesthesia during administration as well as rebound insomnia following its abrupt discontinuation.

6. Benefit/risk assessment

The CPMP expressed concern regarding the effectiveness of zaleplon in sleep maintenance. Review of the clinical trial data in this regard did not resolve this concern as no clinically significant effects on sleep duration or quality of sleep had been demonstrated. By contrast zaleplon had been shown to be an effective sleep inducer and had a low propensity to cause carryover effects. These effects were considered to be an inherent property of the pharmacokinetic behaviour of zaleplon, specifically its very short half-life, rather than a novel mechanism of action as compared with other benzodiazepines and benzodiazepine-like agents. In view of its effect on sleep induction rather than sleep maintenance, the CPMP decided that it was necessary to strictly limit the pack sizes to be made available to support a maximum of two weeks administration reflecting the maximum duration of treatment. The indication was also reinforced with a direction to use the product only when the disorder is severe, disabling or subjecting the individual to extreme distress in line with the indications for other benzodiazepines and benzodiazepine-like agents (CPMP recommendation regarding short acting hypnotics, III/5319/93). Appropriate wording of the indication and additional information in the SPC was considered to be sufficient to alert the prescriber to its potential reduced effectiveness in sleep maintenance and the need to switch to alternative therapy if early morning awakening is experienced.

As for the pharmacodynamic and safety data zaleplon appeared to have benzodiazepine properties, suitable warnings concerning the possibility of rebound, withdrawal, amnesia and paradoxical effects similar for all the benzodiazepines were included in the SPC.

A further concern was expressed by the CPMP regarding the potential misuse of zaleplon by covert administration to others. Zaleplon is quick acting, short-lived, is in a capsule formulation and has little taste. Thus is could be easily administered to an unknowing victim in a drink. In response to this concern the applicant reformulated the product to introduce two markers so that if the capsule is dissolved in liquid the liquid changes colour and becomes cloudy. A statement to this effect is included in the patient information leaflet. The CPMP concluded that this was an acceptable approach to address this issue.

The legal status classification for zaleplon was discussed by the CPMP in the light of consideration of its abuse potential relative to other benzodiazepines and benzodiazepine-like compounds. The CPMP

recommended that zaleplon should be classified as a "medicinal product subject to medicinal prescription" and did not consider that there were grounds for applying a more restrictive legal status such as "medicinal product subject to special medical prescription" as zaleplon is not listed in the United Nations Psychotropic Convention nor is its abuse potential likely to be any greater than other benzodiazepine and benzodiazepeine-like compounds currently registered in Europe with a similar classification.

A divergent view was expressed by some CPMP members who considered that the legal status classification for zaleplon should be "medicinal product subject to special medical prescription" as it contains a substance which by reason of its novelty and properties could be considered as belonging to the substances defined in Article 3 (2) of Directive 92/26/EEC as a precautionary measure. Moreover, they considered that if incorrectly used zaleplon is likely to present a risk of medicinal abuse.

Based on the available data on quality, safety and efficacy, the CPMP considered by a majority of 24 out of 26 votes that the benefit/risk profile of Sonata for the following indication was considered favourable:

"Zaleplon is indicated for the treatment of patients with insomnia who have difficulty falling asleep. It is indicated only when the disorder is severe, disabling or subjecting the individual to extreme distress."