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Benefit-Risk Assessment of Zaleplon in the Treatment of Insomnia

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Abstract

Insomnia is a heterogeneous, highly prevalent condition that is associated with a high level of psychiatric, physical, social and economic morbidity. The treatment of insomnia involves pharmacological and non-pharmacological interventions. The mainstay of pharmacological treatment of insomnia has been the benzodiazepines, the introduction of which represented a significant improvement over the barbiturates and chloral hydrate. Although benzodiazepines have been shown to be efficacious in treating insomnia, they have also been associated with a number of adverse effects including tolerance, dependence, withdrawal and abuse potential, impairment in daytime cognitive and psychomotor performance (including an increased risk of accidents and falls), adverse effects on respiration and the disruption of normal sleep architecture with reduction in both slow wave sleep and rapid eye movement. In the last decade, the treatment of insomnia has

been supplemented by the introduction of a number of non-benzodiazepine hypnotics including zolpidem, zopiclone and, most recently, zaleplon.

Zaleplon possesses a unique pharmacological profile, with an ultra-short half-life of about 1 hour, and selective binding to the $BZ_1(\omega_1)$ receptor subtypes of the $GABA_A$ receptor. This unique pharmacological profile predicts a number of pharmacodynamic properties that account for a unique benefit-risk profile. Consistent with these predictions, zaleplon has been shown in a number of studies to be efficacious in promoting sleep initiation, but less so in promoting sleep maintenance. The adverse effects associated with zaleplon have been shown to be more rapidly resolved and/or lesser in magnitude than those associated with benzodiazepines (including triazolam) and the longer acting non-benzodiazepine hypnotics (zolpidem and zopiclone). This improved risk profile includes: the effects of zaleplon on psychomotor and cognitive performance; tolerance, withdrawal and rebound; respiratory depression; sleep architecture; and other treatment-emergent adverse effects. The unique benefit-risk profile of this agent may be particularly suitable for certain patients with insomnia and provides yet another option in the management of this impairing condition.

Insomnia is a highly prevalent phenomenon with a high level of psychiatric, physical and social disability. Although multiple pharmacological agents have been employed in treating this debilitating condition, the benefits associated with such agents, in terms of increasing nocturnal sleep, have been offset by the a number of untoward effects in keeping with their sedative properties, in particular residual daytime sleepiness and cognitive impairment. Sleep maintenance insomnia has proven particularly difficult to treat in this regard, with clinicians having to find a balance between agents that are effective throughout the night, while minimising next-day effects. In recent years, zaleplon, an ultra-short-acting hypnotic, has been developed as a means of providing insomnia relief without residual daytime effects, including with middle-of-the-night use. This paper reviews the evidence supporting the clinical efficacy and safety of zaleplon as a treatment for the heterogeneous phenomenon of insomnia.

A Medline search (1966–June 2004) was performed to identify clinical studies, case reports, abstracts and reviews that provided data on zaleplon with respect to both its efficacy and safety. The key words included ‘zaleplon’, ‘CL284,846’ and ‘insomnia’. Additional references were obtained from cited articles in the identified papers. No restrictions were made as to the date or type of publication, although emphasis was given to clinical studies with sound methodology.

1. Insomnia: Definition, Consequences and Treatment

Insomnia is a heterogeneous phenomenon that is characterised by difficulties in initiating sleep, maintaining sleep (with frequent or prolonged awakenings), early morning awakening, or even non-restorative or diminished quality of sleep in the face of seemingly adequate sleep duration. Little formal attention has been paid to the notion of ‘sleep fragmentation’ with multiple short arousals. This often presents with daytime sleepiness. This is in contradistinction to many patients with insomnia who have a hyperarousal that allows for daytime alertness (although often with fatigue as opposed to sleepiness) notwithstanding disrupted nocturnal sleep. ‘Sleep fragmentation’ and the accompanying hypersomnolence often respond well to hypnotics. For the patient, this often seems paradoxical (a sleeping pill for a sleepy person), but even the most ‘recalcitrant’ can be persuaded when provided with a rationale. Sleep difficulties as a whole may be situational or episodic, transient, acute or even

chronic and last for several months to years. Nocturnal disturbances are in turn accompanied by a number of residual daytime effects, including fatigue, decreased energy, poor concentration, memory impairment, reduced efficiency in performing complex tasks and mood disturbances such as irritability or depression.[1-3]

In this regard insomnia may be seen as a symptom that is produced by a number of underlying medical, psychiatric and primary sleep disorders, as well as environmental, behavioural and substance dependent factors. In the absence of such underlying conditions, the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)[4] does allow for the diagnosis of 'primary insomnia', whereas the International Classification of Sleep Disorders[5] recognises three intrinsic insomnias, including 'idiopathic insomnia', 'psychophysiologic insomnia' and 'sleep state misperception'. Even in the case of a primary or intrinsic insomnia, a number of physiological, cognitive, affective and behavioural factors are presumed to be causative in terms of the underlying aetiology.

Insomnia is a prevalent health complaint, although given its heterogeneity, prevalence estimates vary largely in accordance with the definitions and criteria used. Ohayon,[6] in an extensive review of epidemiological studies of insomnia, estimated that 33% of the general population will experience insomnia symptoms at any one time, 9–15% will experience insomnia symptoms accompanied by daytime sequela, 8–18% express dissatisfaction with their sleep and 6% will meet the DSM-IV criteria for insomnia. Insomnia is more prevalent in women, older adults and in patients with medical or psychiatric disorders.[1]

Chronic insomnia, in accordance with its effects on daytime functioning and performance, is associated with significant psychosocial, occupational, health and economic morbidity. A strong correlation exists between insomnia and psychiatric disorders, in particular depression, and various psychological symptoms. Likewise a high correlation exists between insomnia and overall poor health.[7] For example, a meta-analysis conducted by Schwartz et al.[8] demonstrated an increased risk of coronary artery disease in association with insomnia, independent of other known risk factors. Although cause and effect relationships between insomnia and psychiatric or medical disorders remain indeterminate, bidirectional influences are not unlikely. Insomnia is also associated with increased psychological stress, decreased ability to cope with stress, higher rates of work absenteeism, decreased productivity, higher rates of accidents, increased general medical services utilisation and decreased overall quality of life.[7,9,10] Chilcott and Shapiro[11] estimated the direct, indirect and related costs of insomnia and its treatment in the US to range from $US30 billion to $US35 billion annually (1994).

These considerations argue for the acceptance of insomnia as a serious medical condition and for its optimal management and treatment. The management of insomnia should begin with addressing any underlying factors that contribute to disturbed sleep, followed by interventions, both non-pharmacological and pharmacological, that directly target the insomnia itself.

A number of non-pharmacological techniques have been shown to be particularly effective in the treatment of insomnia, including stimulus control, so-called sleep restriction (which is in fact 'bed restriction'), relaxation techniques, sleep hygiene education and cognitive therapy. There are also a number of non-pharmacological techniques that show promise, including art therapy,[12] music therapy[13,14] and group therapy.[15] Such interventions have been shown to be as effective as pharmacotherapy in the short term and perhaps more so over sustained periods of time.[16,17] However, such interventions are also time consuming and costly, require a high degree of patient motivation and may prove impractical for widespread utilisation. Furthermore, a combination of pharmacological and non-pharmacological techniques may be particularly effective in individual patients, particularly those with chronic, debilitating insomnia.

The mainstay of pharmacological treatment for insomnia over the past 30 years has been the benzodiazepines, primarily owing to their overall superior

benefit-risk profile in comparison with the barbiturates and chloral hydrate. Based on their pharmacokinetic profiles and duration of action, benzodiazepines are commonly divided into three classes: short-acting (triazolam, midazolam), intermediate-acting (lorazepam, temazepam) and long-acting (clonazepam, nitrazepam, flurazepam). The actions of all benzodiazepines are mediated through non-selective activation of the $BZ_1(\omega_1)$ and $BZ_2(\omega_2)$ receptor subtypes of the $GABA_A$ receptor complex, which accounts for their hypnosedative, anxiolytic, anti-convulsant and myorelaxant properties, as well as their cognitive and psychomotor effects. It is felt that activity at the $BZ_1(\omega_1)$ receptor specifically mediates the sedative-hypnotic properties of these drugs. Benzodiazepines have been shown to be effective in increasing sleep duration.[18] However, they have also been associated with a number of adverse effects, including tolerance, dependence, withdrawal and abuse potential, impairment in daytime cognitive and psychomotor performance (including an increased risk of accidents and falls), adverse effects on respiration and disruption of normal sleep architecture with a reduction in both slow wave sleep and rapid eye movement (REM).[1,2]

The treatment of insomnia has advanced in the last decade, with the introduction of a series of non-benzodiazepine sedative-hypnotics that demonstrate greater selectivity for the $BZ_1(\omega_1)$ receptor subtype, thus retaining the hypnosedative properties of the benzodiazepines, while avoiding their adverse effects. This next generation of hypnotics includes zopiclone, zolpidem and, most recently, zaleplon.

2. Pharmacological Profile

Zaleplon (CL284,846), a pyrazolopyrimidine, is a novel, non-benzodiazepine sedative-hypnotic that, like zolpidem, has been shown to be highly selective for the $BZ_1(\omega_1)$ receptor subtype.[19-23] However, zaleplon may have a lower affinity for the receptor than zolpidem.[21] In humans, zaleplon is quickly and almost completely absorbed, with a time to peak onset (t_{max}) of approximately 1 hour after oral administration.[24-27] The drug undergoes significant first pass metabolism, with a low absolute bioavailability of 30%.[27] Metabolism of zaleplon occurs in the liver, primarily by aldehyde oxidase and secondarily by cytochrome P450 (CYP) 3A4, into a number of pharmacologically inactive compounds, including 5-oxo-zaleplon, desethylzaleplon and 5-oxo-desethylzaleplon. These compounds undergo further metabolism by conjugation before being eliminated in the urine. Less than 1% of zaleplon is excreted unchanged in the urine.[27] Zaleplon is extensively and rapidly eliminated with an elimination half life ($t_{1/2}$) of approximately 1 hour.[24-27] By comparison, the $t_{1/2}$ of triazolam is approximately 2.5 hours, of zolpidem is 2–2.2 hours and of zopiclone is 4–5 hours.[2,28] The oral clearance of zaleplon has been shown to be significantly reduced in patients with liver disease,[29] but not in those with renal dysfunction,[30] nor in the elderly.[31] The recommended dose of zaleplon 10mg in adults and 5mg in the elderly.[2]

The unique pharmacological profile of zaleplon predicts that at therapeutic doses it should be effective in reducing sleep onset latency but less effective in maintaining sleep. Its selective pharmacodynamic profile and short half-life should also confer limited or no next-day residual effects when administered in the evening or middle of the night, in comparison with both benzodiazepines and longer acting non-benzodiazepines (zolpidem, zopiclone). Indeed, a number of studies have born out this predicted benefit-risk profile.

3. Therapeutic Efficacy

3.1 Primary Insomnia

In an early double-blind, placebo-controlled study, Walsh et al.[32] investigated the efficacy and tolerability of zaleplon 5mg and 10mg in a group of 132 patients with primary insomnia for a period of 14 days. Triazolam 0.25mg was used as an active comparator. Zaleplon 5mg and 10mg both significantly shortened the latency to persistent sleep in comparison with placebo on a polysomnographic (PSG) recording done on the first 2 nights of treatment (17.0 minutes, 19.3 minutes and 25.4 minutes, respectively). Although the response to zaleplon

remained persistent throughout the 2 weeks of the trial, the effects of either dose were no longer statistically significant on a PSG recording done on the final 2 nights, primarily owing to an improvement in the placebo group. Total sleep time and the number of awakenings were not affected by either zaleplon dose. Subjective measures, in general, supported the PSG data but were significant only for zaleplon 10mg. Trizaolam in comparison with placebo produced similar effects to zaleplon, but with an additional improvement in total sleep time at the beginning of the study.

In another study, Drake et al.[33] employed triazolam 0.25mg as an active comparator in a 2-night treatment protocol in two groups of 36 and 47 patients with chronic primary insomnia. They found that zaleplon 10mg, 20mg, 40mg and 60mg all significantly reduced the time to sleep onset in comparison with placebo (on PSG and subjective measures), with only zaleplon 40mg and 60mg proving more efficacious in this regard than triazolam 0.25mg. Only zaleplon 60mg significantly increased total sleep time in comparison to placebo, whereas triazolam did so in comparison to all other treatments.

Elie et al.[34] investigated the efficacy and tolerability of zaleplon 5mg, 10mg and 20mg in comparison with placebo in a group of 574 patients with primary insomnia over a period of 4 weeks, with zolpidem 10mg as an active comparator. Subjective measurements of sleep variables were determined from daily post-sleep questionnaires and averaged for each week of double-blind treatment. Median sleep latency was significantly reduced for all zaleplon doses during week 1 (21–24 minutes shorter from baseline in the zaleplon groups vs 8 minutes shorter in the placebo group), with a significant dose trend. This significant decrease persisted for zaleplon 5mg up to week 3 and for zaleplon 10mg and 20mg throughout the 4 weeks, despite a progressive reduction in median sleep latency in the placebo group (such that the difference in median sleep latency between the zaleplon and placebo groups at the end of 4 weeks was about 5 minutes). Only zaleplon 20mg produced a significant, albeit modest, increase in total sleep time in comparison with placebo and did so in all weeks except week 3. In comparison, zolpidem 10mg significantly decreased sleep latency during the first 3 weeks and increased sleep duration in all weeks of treatment. Mixed results were seen in all treatment groups with respect to sleep quality (with greater improvement with zolpidem 10mg) and no treatment affected the number of awakenings during the night.

In a similar 4-week, placebo-controlled trial, Fry et al.[35] investigated the effects of zaleplon 5mg, 10mg and 20mg in a groups of 586 patients with primary insomnia, with zolpidem 10mg as the active comparator. Subjective sleep measures were derived from daily post-sleep questionnaires and were averaged on a weekly basis. Subjective sleep latency was significantly reduced in all zaleplon groups at week 1 (with a 15–25 minute difference in reductions from baseline between the zaleplon and placebo groups), an effect that persisted in absolute terms, but remained statistically significant only for zaleplon 20mg during all 4 weeks and for zaleplon 10mg at week 3. As in previous studies, the long-term effect of zaleplon in comparison with placebo was mitigated by a significant placebo response. Variable significant effects in subjective total sleep time, number of awakenings and sleep quality were seen only in the zaleplon 20mg group. Zolpidem reduced sleep latency only on week 1 and 4, but had more consistent effects on total sleep time and sleep quality.

Walsh et al.[36] studied the efficacy of zaleplon 10mg in comparison with placebo in 113 patients with primary insomnia over a period of 5 weeks, which was the longest such trial to date. Regular PSGs and post-sleep questionnaires were employed. PSG data indicated a significant improvement in the latency to persistent sleep for zaleplon 10mg during all 5 weeks in comparison with placebo. Throughout the trial median latency to persistent sleep was 22–25 minutes shorter than baseline in the zaleplon group versus 9.5–16 minutes in the placebo control group. No consistent treatment effects were seen in terms of total sleep time, number of awakenings or wake time after sleep onset. Subjective sleep mea-

sures supported findings obtained through PSG recording.

3.2 'As Needed' Use

Although middle-of-the-night 'as needed' use has often been advocated as an indication for zaleplon, few studies have specifically evaluated its efficacy in this regard. Corser et al.[37] reported the effects of zaleplon 10mg, zolpidem 10mg and placebo when administered in a group of 32 healthy sleep maintenance insomniacs who were awakened 4 hours after lights out on 2 consecutive, PSG recorded, nights. Zaleplon 10mg significantly decreased the latency to persistent sleep and increased the total sleep time, with an effect comparable to zolpidem 10mg.

Stone et al.,[38] in an experimental, noise-induced model of situational insomnia, investigated the effects of middle-of-the-night administration of zaleplon 10mg and 20mg, zopiclone 7.5mg and placebo on a single, PSG recorded, night in a group of 13 normal subjects. Subjects were awakened after 5 hours of sleep and subjected to a sound stimulus designed to increase sleep latency. Latency to persistent sleep was significantly shorter (about 9–14 minutes) in both the zaleplon 10mg and 20mg groups than with placebo, an effect not seen with zopiclone.

3.3 Elderly

A number of studies have also demonstrated the efficacy and safety of zaleplon in elderly patients with insomnia. Walsh et al.[39] examined the effects of zaleplon 2mg, 5mg and 10mg in a group of 48 elderly patients in a double-blind, placebo-controlled, crossover study. PSG recording and post-sleep questionnaires were employed over 2 days for each treatment. Significantly decreased latency to persistent sleep was seen in all the zaleplon groups on PSG recording (3–15 minutes shorter than placebo) and in the zaleplon 5mg and 10mg groups on subjective estimates. Total sleep time was significantly increased on PSG recording in the zaleplon 5mg and 10mg groups (by about 20–30 minutes more than placebo), but only in the zaleplon 10mg group on subjective assessment. No treatment effect was seen in the number of awakenings or subjective sleep quality.

Hedner et al.[40] studied the effect of zaleplon 5mg and 10mg in 422 elderly patients with chronic primary insomnia over a period of 2 weeks using post-sleep questionnaires. Subjective sleep latency was significantly decreased for zaleplon 5mg and 10mg in comparison with placebo over both weeks of treatment (despite a progressive placebo response). Subjective sleep quality was also increased for both zaleplon doses over both weeks. Subjective total sleep time and number of awakenings were only significantly affected by zaleplon 10mg during the first week.

In a similar study, Ancoli-Israel et al.[41] investigated the effects of zaleplon 5mg and 10mg in comparison with placebo in a group of 549 elderly patients with primary insomnia over a period of two weeks, with zolpidem 5mg as an active comparator. Zaleplon 10mg significantly reduced subjective sleep onset latency on both treatment weeks, whereas zaleplon 5mg did so only on week 2. Increased subjective total sleep time was increased only with zaleplon 10mg during week 1. In contrast, zolpidem 5 mg decreased subjective sleep latency, increased total sleep time and decreased the number of awakenings during the night on both treatment weeks.

3.4 Summary

In summary, a number of studies have demonstrated the efficacy of zaleplon in reducing sleep latency with an effect comparable to triazolam, zolpidem and zopiclone, at least with doses equal to or above the recommended dose of 10mg. This efficacy has been studied mainly in regular evening use over a period of 2–5 weeks with PSG recording and subjective sleep measures.[32,34-36] In these trials, a treatment effect of zaleplon is generally noted within the first week and remains relatively stable throughout treatment. However, absolute differences from placebo lessened over time in most studies, owing to a progressive placebo response. Walsh et al.[36] commented on the fact that this may not

only be due to a true placebo effect, but also to the required adherence to protocol restrictions associated with insomnia studies, such as regular sleep schedules and limitations on caffeine, etc, which in themselves represent significant behavioural interventions. Although the effects of zaleplon may be said to be somewhat modest, particularly with continued use, this does not mitigate its usefulness in selected patients. Middle-of-the-night use of zaleplon, while frequently advocated, has been less studied in terms of its efficacy, with an absence of studies lasting more than 2 nights.

Although it consistently demonstrates a reduction in sleep onset latency, zaleplon 10mg has relatively little effect on the total sleep time or number of nocturnal awakenings, which is consistent with its pharmacological profile. Minimal effects were observed with zaleplon 20mg, but no more than with triazolam 0.25mg or zolpidem 10mg. Reported effects of zaleplon on sleep quality were variable and inconsistent.

Zaleplon has been shown to be effective in the elderly with respect to reducing sleep latency, with a lesser effect on total sleep time and number of nocturnal awakenings. As expected, the elderly population demonstrated an increased sensitivity to lower doses of zaleplon. There are no studies that have evaluated the efficacy of middle-of-the-night use of zaleplon in the elderly, which is an unfortunate deficit given the prevalence of early morning awakening in this group.

4. Safety Profile

A number of articles have considered the safety of zaleplon, specifically in comparison with the adverse effects that have proven to be problematic with the benzodiazepines. Similarly, other studies have looked at the effects of zaleplon with regard to psychomotor and memory impairment, driving impairment, tolerance, rebound and withdrawal, abuse potential, alcohol potentiation, drug interactions, sleep architecture, respiratory depression and treatment emergent adverse effects.

4.1 Psychomotor and Memory Impairment

4.1.1 Awake

A number of studies have investigated the immediate and short-term effects of zaleplon on psychomotor function and memory when administered to patients who are awake. Beer et al.,[24] in an early evaluation of zaleplon in humans, looked at the effects of single doses of 1mg, 5mg, 15mg, 30mg and 60mg in a randomised, double-blind, parallel study involving 38 healthy volunteers. Consistent impairment of psychomotor performance was only seen with zaleplon 60mg and, to a lesser extent, zaleplon 30mg on a variety of tasks, including the continuous attention test, critical flicker fusion, choice reaction time, the Salford tracking test and a word recall test. These effects were generally self limiting, as they were confined to the 2.5-hour post-treatment period, and roughly paralleled subjective measures of drowsiness and plasma concentrations of the drug as determined by a concurrent pharmacokinetic analysis. No effect on napping was seen after 3.5-hours post-administration.

Allen et al.[42] compared the effects of single doses of zaleplon 20mg and lorazepam 2mg in 12 healthy men in a randomised, placebo-controlled, crossover study. Performance on a comprehensive battery of psychomotor and memory tests (working and secondary) were assessed at pre-treatment and at 1, 3 and 5 hours post-treatment. In general, both zaleplon 20mg and lorazepam 2mg produced similar impairments on memory tasks (including digit span, Baddeley reasoning task, mental rotation, free recall, sentence verification task, prose recall and pursuit rotor) at 1-hour post-treatment. However, recovery was more rapid with zaleplon, with less adverse effects and was generally similar to placebo at 3 hours, in comparison with a more persistent effect of lorazepam of up to 5 hours. Performance on psychomotor tasks (including tapping rate, focused attention, rapid information processing task, digit symbol substitution, copying tests and critical flicker fusion threshold) showed a similar trend of impairment and recovery, but with less marked impairment with zaleplon 20mg in comparison with placebo beginning at the 1-hour mark. This was despite

similar levels of subjective drowsiness with the two treatments.

Rush et al.[43] compared the effects of single, daytime doses of zaleplon 25mg, 50mg and 75mg and triazolam 0.25mg, 0.5mg and 0.75mg in a group of 14 subjects with a history of drug abuse. A battery of psychomotor and memory tests was conducted at regular intervals (up to 24 hours post-dose), including tests of digit symbol substitution, circular lights, balance, repeated acquisition, digit-enter-recall, picture recall and recognition. Zaleplon and triazolam, over the given dose ranges, were felt to produce comparable dose-dependent task impairments, with generally the highest two doses differing significantly from placebo (but with some additional impairment noted with zaleplon 25mg). Zaleplon, in comparison with triazolam, was judged to have a more rapid onset of action (0.5 hour vs 1 hour), a more rapid time to peak effect (0.5–1 hour vs 2 hours) and shorter duration of action (2–3 hours vs 4–6 hours), despite the higher-than-recommended doses of zaleplon employed.

Greenblatt et al.[26] investigated the effects of single doses of zaleplon 10mg and 20mg and zolpidem 10mg and 20mg in a double-blind, placebo-controlled crossover study involving 10 healthy men. Only zolpidem 20mg produced a significant difference from placebo on subjective and observer-rated measures of sedation, and impairment on the digit symbol substitution over 4 hours. Both zolpidem 10mg and 20mg significantly impaired free recall at 24 hours of a word list learned at 1.5 hours. Zolpidem 20mg also significantly reduced initial learning of a word list at 1.5 hours. Significant differences between treatments were found on most measures, with less pronounced effects with zaleplon 10mg and 20mg than with zolpidem 10mg and 20mg, but with zaleplon 20mg and zolpidem 10mg being comparable on some measures. Treatment effects on sedation and the digit symbol substitution test also paralleled increases in beta EEG activity and drug plasma concentrations as analysed during a concurrent pharmacokinetic study.

Drover et al.[25] found that zaleplon 10mg and 20mg and zolpidem 10mg and 20mg all significantly impaired performance in comparison with placebo on the digit symbol substitution test for up to 5 hours post-dose in a group of 10 healthy subjects. However, impairment was significantly greater in the zolpidem groups than with zaleplon in the first 4 hours. No impairment was seen with zaleplon on a word list test of immediate and remote recall, whereas zolpidem impaired recent recall at 1.5 hours and 8 hours post-dose, and remote recall at 8 hours. Zolpidem also produced greater levels of objective and subjective sedation scores, with recovery to baseline after 8 hours versus 4 hours for those in the zaleplon groups. These effects also paralleled the results of a simultaneously performed pharmacokinetic study.

Paul et al.[44] recently reported on a placebo-controlled, crossover study investigating the effects of single doses of morning zaleplon 10mg, zopiclone 7.5mg, temazepam 15mg and time released melatonin in 23 healthy subjects. The serial reaction test, logical reasoning test, serial subtraction test and multitask test battery were performed at regular intervals up to 7 hours post-dose. Zaleplon 10mg, zopiclone 7.5mg and temazepam 15mg produced impairment on all four tasks, with zaleplon being associated with the quickest recovery (within 2.25–3.25 hours). Interestingly, melatonin was not associated with impairment on any test, despite persistent subjective sleepiness.

4.1.2 Evening/Middle of the Night

A number of short-term studies have examined the residual effects of evening and middle-of-the-night administration of zaleplon in subjects allowed to sleep. Troy et al.[45] looked at the cognitive effects of single night-time doses of zaleplon 10mg and 20mg, zolpidem 10mg and 20mg and triazolam 0.25mg in 24 healthy young adults. A battery of memory and cognitive tests was administered 1.25 hours and 8.25 hours post-dose, including the digit symbol substitution test, immediate and delayed word recall tests, digit span test, paired associates learning test and divided attention test. At 1.25 hours post-dose, only zaleplon 10mg exhibited no impairment on any of the performed tests, in comparison with placebo, with other treatments exhibit-

ing impairment on a number of measures (with triazolam 0.25mg fairing the best, zaleplon 20mg comparable to zolpidem 10mg and zolpidem 20mg fairing the worst). At 8.25 hours post-dose, zaleplon 10mg and 20mg and zolpidem 10mg exhibited continued impairment on delayed word recall (but not on a 'retention score' with zaleplon 10mg). Zolpidem 20mg and triazolam 0.25mg produced continued impairment on delayed word recall and the digit symbol substitution test. Notably the therapeutic dose of zolpidem (10mg) was found to be significantly more impairing than the therapeutic dose of zaleplon (10mg) on a number of measures, both 1.25 hours and 8.25 hours post-dose.

Drake et al.,[33] in the 2-night study on patients with chronic insomnia noted in section 3, found no significant effects of zaleplon 10mg, 20mg, 40mg and 60mg administered in the evening with respect to morning performance on a number of tests, including the digit symbol substitution test, digit copying test and digit span test. In contrast, impairment was seen on the digit copying test with triazolam 0.25mg, albeit inconsistently.

Vermeeren et al.[46] compared the effects of zaleplon 10mg and 20mg with zopiclone 7.5mg when administered in the evening or middle of the night in a double-blind, 7-way crossover study involving 28 healthy volunteers. Evening doses were given prior to initiating sleep and middle-of-the-night doses were given 5 hours after sleep onset, followed by an additional 3 hours of sleep. A test battery was initiated 45 minutes after awakening, which corresponded to 8.75 hours after the evening dose and 3.75 hours after the middle-of-the-night administration. A standardised, actual driving test was also administered after the test battery. Evening doses of zaleplon 10mg and 20mg had no significant effects in comparison with placebo on all measures, including body sway, word leaning (immediate recall, delayed recall and recognition), spatial memory, syntactic reasoning and semantic verification. Middle-of-the-night zaleplon 10mg and 20mg only impaired delayed word recall (but not recognition). Evening zopiclone 7.5mg impaired performance on the delayed word recall test and, when given in the middle of the night, significantly affected body sway and "practically every memory parameter". Both evening and middle-of-the-night zopiclone significantly impaired driving performance, an effect not seen with zaleplon.

In a follow-up study Vermeeren et al.[47] found no residual effects of evening zaleplon 10mg on a number of morning (10 hours after administration) psychomotor and memory tasks, including the word learning test, critical tracking test and the divided attention test. Evening zopiclone 7.5 mg, in contrast, was associated with significant impairment on all word leaning parameters (immediate recall, delayed recall, relative recall and recognition score and speed), as well as with divided attention. Zopiclone 7.5mg was also associated with significant driving impairment, whereas zaleplon was free of such an effect (see section 4.2).

Stone et al.,[38] in the single night noise-induced, sleep-maintenance protocol cited in section 3, administered a test battery 4 hours after middle-of-the-night administration (5 hours after bedtime). Although significantly decreasing latency to persistent sleep, neither zaleplon 10mg or 20mg produced significant residual effects in comparison with placebo, as assessed by performance on the digit symbol substitution test, choice reaction time test, critical flicker fusion test, word list test (immediate and delayed word recall) and subjectively assessed sedation. Middle-of-the-night zopiclone 7.5mg, on the other hand, produced impairment with respect to the digit substitution test, choice reaction time test and delayed word recall test, despite a lack of significantly increased subjective sedation.

Walsh et al.[48] investigated the effects of zaleplon 10mg and flurazepam 30mg in comparison with placebo in a group of 22 healthy sleep maintenance insomniacs, with treatment or placebo administered 3.5 hours after bedtime for 2 consecutive, PSG recorded, nights. A battery, including a nap opportunity, was performed at 5 hours and 6.5 hours after middle-of-the-night drug administration (3.5 hours after bedtime). In comparison with placebo, zaleplon 10mg produced no residual effects at 5 hours and 6.5 hours with respect to nap sleep laten-

cy, subjective sleepiness and performance on the digit symbol substitution test and symbol copying test. Flurazepam 30mg, the active comparator, at both 5 hours and 6.5 hours post-dose, significantly decreased nap sleep latency, increased subjective sleepiness and impaired performance on the digit symbol substitution test and symbol copying test, in comparison with both placebo and zaleplon. However, the clinical validity of these findings can be questioned, given the use of a higher-than-recommended dose of a long acting benzodiazepine as the active comparator to zaleplon for middle-of-the-night use.

Verster et al.[49] performed a double-blind, placebo-controlled, crossover trial to compare the residual effects of middle-of-the-night administration of zaleplon 10mg and 20mg and zolpidem 10mg and 20mg in 30 healthy volunteers. Treatment was given after 5 hours of sleep, followed by an additional 3 hours of sleep. A standard driving test was performed at a time corresponding to 4 hours post-dose, followed by a test battery at 6 hours post-dose. Zolpidem 20mg was associated with significant impairment on all psychomotor and memory tasks, including the digit symbol substitution, critical tracking test, divided attention test and word list test. No impairment was seen on any of these tasks with zolpidem 10mg and zaleplon 10mg and 20mg, in comparison with placebo. In a separate study on the same subject group, ethanol at a blood alcohol concentration (BAC) of 0.05% significantly impaired performance on a number of the same psychomotor and memory tasks. Both doses of zolpidem were also associated with driving impairment, whereas zaleplon was free of these effects (see section 4.2).

Corser et al.[37] reported the next-day residual effects of zaleplon 10mg and zolpidem 10mg, given 4 hours after bedtime over two consecutive nights, in a group of 32 patients with sleep maintenance insomnia. In comparison with placebo, zolpidem 10mg was associated with significant impairment on the digit symbol substitution, decreased subjective level of alertness and ability to concentrate, and shortened sleep latency time on next-day napping for up to 4–7 hours after administration. No such impairment was seen with zaleplon 10mg.

Danjou et al.[50] examined the effects of single doses of zaleplon 10mg and zolpidem 10mg in comparison with placebo in 36 healthy subjects, with doses given at predetermined times 5, 4, 3 or 2 hours before morning awakening (which occurred 8 hours after bedtime). Residual effects were assessed via a test battery that included the digit symbol substitution test, choice reaction time, critical flicker fusion threshold, a word list test (immediate and delayed free word recall) and Sternberg memory scanning test. Zaleplon 10mg, regardless of the time of administration (i.e. up to 2 hours before awakening), was not associated with significant impairment on any measure in comparison with placebo. Zolpidem 10mg, by comparison, generally resulted in impairment on most measures when given up to 4–5 hours before awakening (in particular digit symbol substitution and memory tests).

In a similar study, Hindmarch et al.[51] administered zaleplon 10mg and 20mg, zolpidem 20mg and placebo 1, 3 and 5 hours prior to awakening (which occurred 8 hours after bedtime) to a group of 40 healthy subjects. Zaleplon 10mg was devoid of psychomotor or cognitive impairment, aside from a small but significant decrease in digit symbol substitution test scores, when administered 1 hour prior to awakening. Zaleplon 20mg produced no residual effects when administered at 3 and 5 hours prior to awakening, but when administered 1 hour prior to awakening produced impairment on the digit symbol substitution test, choice reaction time, critical flicker fusion threshold and decreased immediate and delayed free word recall. In general, zolpidem 10mg impaired performance on most tests when administered 1 and 3 hours before awakening, and impaired recognition reaction time and delayed free word recall when administered 5 hours before awakening. Overall, zolpidem 10mg produced greater impairment than both doses of zaleplon.

Of the long-term efficacy studies discussed in section 3, only Walsh et al.[32] investigated the residual effects of evening administration zaleplon 5mg and 10mg over 2 weeks of treatment. No daytime

residual effects were observed in either zaleplon dose in comparison with placebo on a number of morning psychomotor and memory tests including the digit symbol substitution test, digit span, simple and complex reaction time and delayed word recall. Triazolam 0.25mg was also associated with a similar lack of impairment and, in fact, produced an improvement in digit symbol substitution test performance in comparison with placebo. It can be interpreted that this is an indication that improved sleep leads to improved psychomotor and cognitive performance. This has wide ramifications, not only for patients with insomnia, but in other patient groups as well, such as patients with depression.

4.1.3 Elderly

Only one study has looked at the residual effect of zaleplon on elderly subjects. Walsh et al.[39] found no significant residual effects of zaleplon 2mg, 5mg and 10mg in a group of elderly patients with insomnia who were treated over 2 nights, as was measured by morning simple reaction time, complex reaction time and digit symbol substitution test.

4.1.4 Summary

In summary, a number of studies have demonstrated that zaleplon, when administered during the day, evening or middle of the night, is associated with less psychomotor and memory impairment and in particular a more rapid recovery, than what are considered equivalent doses of triazolam, zolpidem and zopiclone. Zaleplon 10mg, in particular, seems to be free of residual effects when administered at least 2 hours before rising time. A number of limitations exist in the studies to date. It may be argued that the clinical significance of several of the studies is limited by unfairly comparing zaleplon with intermediate acting agents. However, for the most part, efforts have been made to choose comparators that are commonly prescribed hypnotics (e.g. lorazepam and zopiclone), at standard doses that are felt to be relatively free of next-day residual effects. In general, most studies have only looked at the residual effects of zaleplon during short-term use (1–2 nights). Longer studies may prove to mitigate differences in residual effects between zaleplon and longer acting agents (e.g. zolpidem), as tolerance for the latter might be expected to occur. Most of the cited studies have also been performed on healthy subjects, which mitigates the improvements on psychomotor and memory performance that might be expected to occur in successfully treated insomniacs, particularly with longer acting hypnotics that promote sleep maintenance in addition to sleep initiation. Indeed Walsh et al.,[32] as noted, found no difference in the residual effects of zaleplon in comparison with placebo after 2 weeks of treatment. In the only paper to specifically assess patient preference, Allain et al.,[52] in a group of 53 patients with insomnia, found a self-rated preference for single evening doses of zolpidem 10mg over zaleplon 20mg (62% vs 38%); however, this marked trend did not reach statistical significance. The reasons for patient preference for zolpidem over zaleplon were not directly questioned, but it was also found that the subjective quality of sleep and ease of falling asleep were both significantly better with zolpidem and the quality of day life was similar with both zolpidem and zaleplon. Thus, the clinical significance of the observed beneficial safety profile of zaleplon over other hypnotics remains to be proven in longer term studies on patients with insomnia.

4.2 Driving Impairment

In the study cited in section 4.1.2, Vermeeren et al.[46] administered a standardised, actual driving test corresponding to an interval of 10 hours after the evening administration of zaleplon 10mg and 20mg, zopiclone 7.5mg or placebo and 5 hours after middle-of-the-night administration of these agents. The test involved driving, in a specially instrumented car, along a 100km stretch of primary highway circuit at a constant speed (95 km/hour) and steady lateral position. Primary outcome measures were the standard deviation in speed (SDSP) and the standard deviation of lateral position (SDLP). No driving impairment was seen with either evening or middle-of-the-night doses of zaleplon 10mg or 20mg. In contrast, evening zopiclone 7.5mg produced significant impairment in mean SDLP (estimated to be the equivalent of a BAC of 1.0 mg/mL), with even greater impairment and also significantly increased

SDSP seen with middle-of-the-night zopiclone. Using the data from this study and an analytic model of equivalent BAC impairment, Menzin et al.[53] estimated that in comparison with zaleplon, the use of zopiclone over 14 days in France would be expected to result in 503 excess accidents per 100 000 drivers.

In the follow-up study noted in section 4.1.2, Vermeeren et al.[47] administered an identical standardised driving test to 30 healthy subjects 10–11 hours after evening doses of either zaleplon 10mg or zopiclone 7.5mg. Zaleplon 10mg was not associated with significant driving impairment in comparison with placebo, whereas zopiclone 7.5mg significantly increased the mean SDLP in comparison with both placebo and zaleplon. This impairment with zopiclone was significantly worse than that associated with low dose alcohol (BAC 0.05%), the effects of which were tested in a separate part of the study in the same subject group.

Verster et al.[49] administered a similar driving test 4 hours after middle-of-the-night administration of zaleplon and zolpidem. Both zolpidem 10mg and 20mg resulted in a significant, dose-dependent increase in mean SDLP in comparison with placebo (although the effect of zolpidem was felt to be minor). Zolpidem 20mg was associated with an additional significant increase in the SDSP. This impairment in driving was judged to be greater than that produced by the effect of ethanol at a BAC of 0.05%, the effects of which were tested in the same group. No significant impairment in driving ability was seen with middle-of-the-night administration of zaleplon 10mg and 20mg. In addition, Stillwell[54] has recently reported the case of a motor vehicle accident associated with the misuse of zaleplon at a dose of 60mg.

In summary, zaleplon, at doses of 10mg or 20mg that were administered in the evening or middle of the night, appears not to be associated with driving impairment up to 4–5 hours after administration. Zaleplon is notably superior in this regard to both zopiclone and zolpidem, at least after a single nighttime administration.

4.3 Tolerance, Rebound and Withdrawal

In the long-term efficacy studies noted in section 3, the efficacy of zaleplon 5–20mg was found to be relatively persistent over a period of 2–5 weeks and suggested a lack of tolerance over this time period.[32,34-36]

Walsh et al.[36] looked at the potential withdrawal effects of zaleplon during 2 discontinuation nights after 2 weeks of treatment. No discontinuation effects were seen with zaleplon 5mg and 10mg on subjective latency to persistent sleep or total sleep time, on PSG or on subjective measures. The discontinuation of triazolam 0.25mg, in contrast, resulted in increased subjective sleep latency and increased total sleep time on the first, but not the second, night of termination.

Elie et al.[34] measured rebound and withdrawal effects during 3 days of discontinuation of zaleplon 5mg, 10mg and 20mg after 28 days of treatment, via post-sleep questionnaires and the benzodiazepine withdrawal symptom questionnaire (BWSQ).[55] No significant rebound or withdrawal effects in any zaleplon group were observed, aside from some mixed results in the number of awakenings on the second and third discontinuation nights. Zolpidem 10mg, in contrast, exhibited a number of significant rebound and withdrawal effects, although these were confined to the first post-treatment night (which the authors acknowledged would probably only constitute a minor difficulty for patients).

After 28 days of treatment, Fry et al.[35] found little evidence of rebound or withdrawal in zaleplon 5mg, 10mg and 20mg during 3 discontinuation nights. The discontinuation of zolpidem 10mg resulted in a minor decrease in total sleep time (4 minutes) from baseline, significant changes in all sleep variables in comparison with placebo and a greater incidence of withdrawal effects as measured by the BWSQ on the first post-treatment night.

Walsh et al.[48] looked at a number of PSG and subjective sleep measures during two discontinuation nights after 5 weeks of treatment or placebo. No significant differences were seen in latency to persistent sleep, total sleep time or number of awaken-

ings on either discontinuation night with zaleplon 10mg in comparison with placebo or baseline.

Scharf[56] reported that in two open-label, follow-up studies, the effectiveness of zaleplon 10mg was maintained over 12 months of long-term use, with no evidence of significant withdrawal on discontinuation.

Walsh et al.[48] also analysed the minutes of wake time in the last quarter of the 8-hour recording period during treatment and found no difference between zaleplon and placebo; an important consideration given the short half-life of zaleplon. Likewise, Vermeeren et al.[46] found that evening administration of zaleplon had no effect on subjective sleep measures in the second half of the night in comparison with placebo.

In their studies on elderly patients, Hedner et al.[40] found a weak rebound effect on the first night of discontinuation with zaleplon 10mg, with a decrease in subjective total sleep time of 4 minutes in comparison with placebo and a greater number of patients reporting such a decrease. Ancoli-Israel et al.[41] found that discontinuation of zaleplon 10mg produced a significantly decreased subjective total sleep time in comparison with placebo, but only by 2.5 minutes on the first night of withdrawal. Discontinuation of zolpidem 5mg, on the other hand, increased sleep latency by 16 minutes and decreased total sleep time by 17 minutes in comparison with placebo on the first discontinuation night, with a greater number of patients reporting these effects. In neither study was zaleplon 5mg associated with discontinuation effects.

Hedner and Mangano,[57] in an open-label, follow-up study of a group of elderly patients with insomnia, reported continued efficacy of zaleplon 5mg and 10mg over a period of 6–12 months, with little evidence of rebound insomnia after 6 months of use.

4.4 Abuse Potential

Although a lack of tolerance and rebound suggests a lack of physical dependence with respect to the use of zaleplon, few studies have investigated its abuse potential in humans. Beer et al.,[24] in the study mentioned previously, also administered a 'drug liking' questionnaire to a group of healthy subjects at 24 hours post-dose. No significant effects were seen in terms of subjective feelings regarding drug use (like or dislike) and preference to taking the drug again for zaleplon 1mg, 5mg, 15mg, 30mg and 60mg in comparison with placebo.

Rush et al.[43] specifically investigated the abuse potential of zaleplon in comparison with triazolam in a group of 14 subjects with histories of drug abuse (including sedatives and hypnotics) via a series of subjective drug effect questionnaires. The authors concluded that in the dose ranges assessed, zaleplon (25mg, 50mg and 75mg) and triazolam (0.25mg, 0.50mg and 0.75mg) had comparable dose-related effects with respect to abuse potential and behavioural pharmacological profiles. Unfortunately, the recommended dose of zaleplon (10mg) was not assessed. More studies would be warranted before concluding a superiority of zaleplon over other hypnotics with regard to its abuse potential, particularly given its rapid onset and short half-life.

4.5 Alcohol Potentiation

Only one such study has looked at the potentiation of zaleplon-induced cognitive and psychomotor impairment with alcohol coadministration (in humans). Roehrs et al.[58] reported the effects of daytime doses of zaleplon 10mg and triazolam 0.25mg with or without ethanol (0.75 g/kg of bodyweight) in a group of 18 healthy subjects. Treatment was administered in such a way that it would be at peak plasma concentrations at the initiation of a test battery, which was repeated at 1.5 and 3.5 hour intervals thereafter. In general, triazolam without ethanol produced greater and longer lasting impairment than zaleplon without ethanol on a number of measures including digit symbol substitution, symbol copying, simple and complex reaction time, divided attention tracking, central reaction time and peripheral reaction time. Ethanol potentiation was seen with both drugs, but relatively more so with zaleplon 10mg; although, in absolute terms, zaleplon with ethanol produced impairment comparable

to or less than triazaolam with ethanol and for a shorter period of time.

4.6 Drug Interactions

Potentially relevant pharmacodynamic and pharmacokinetic interactions with zaleplon might be expected with other CNS active agents (including sedatives and other psychotropic agents), medications with common metabolic pathways to that of zaleplon (CYP inducers and inhibitors), medications with low therapeutic tolerances (digoxin and warfarin) and those that effect renal excretion (ibuprofen).[59]

Hetta et al.[60] investigated the effects of zaleplon 20mg and thioridazine 50mg, alone and in combination, in a group of 10 healthy subjects. Venous samples were taken at regular intervals and a test battery performed at 1, 2, 4 and 8 hours post-dose. In comparison with the baseline effects of thioridazine alone, the combination of thioridazine and zaleplon produced no additive effects in terms of impaired performance on the critical flicker fusion test and tapping rate, additive effects on a reaction time test at 1 hour and 'supra-additive' effects (greater than the sum of individual effects) on the digit symbol substitution test at 1, 2 and 4 hours, but not 8 hours, post-dose. Coadministration was not found to affect the individual pharmacokinetic profiles of each drug.

Darwish[59] reviewed a number of studies investigating various pharmacological interactions with zaleplon. No pharmacokinetic or pharmacodynamic interactions were found between zaleplon and paroxetine and no pharmacokinetic interactions were found between zaleplon and imipramine, with additive pharmacodynamic effects resolving within 2–4 hours. Diphenhydramine (50mg), a moderate inhibitor of aldehyde oxidase, was not found to affect the pharmacokinetics of zaleplon. Cimetidine (800mg), a moderate inhibitor of both aldehyde oxidase and CYP3A4, was found to decrease the oral-dose clearance of zaleplon by 44% and increase its maximum plasma drug concentration (C_{max}) and area under the concentration-time curve (AUC) by 80%. Zaleplon was also shown to increase the C_{max} of (S-)-warfarin by 17%, but had no effect on the AUC of (S-)-warfarin or the pharmacokinetics of (R+)-warfarin. No prolongation in the international normalised ratio was seen in warfarin-treated patients coadministered zaleplon.

Garcia et al.[61] found no effect of zaleplon 10mg on the pharmacokinetic and pharmacodynamic properties of digoxin 0.375mg in a group of 20 healthy adult men. Garcia et al.[62] also found no pharmacokinetic interactions between zaleplon 10mg and ibuprofen 600mg in 17 healthy subjects.

Höjer et al.[63] have described two cases of medication-induced comas involving large doses of zaleplon: one in combination with alcohol and the other with trimipramine. A recent case report[64] described a suicide by mixed drug intoxication involving high doses of zaleplon, butalbital and alprazolam.

In summary, zaleplon, at doses of 10–20mg, appears to be relatively safe in combination with the medications studied, although a paucity of such studies does exist with zaleplon, even in comparison with the other non-benzodiazepines zolpidem and zopiclone (see Hesse et al.[65] for a review). As Darwish[59] states, the short half-life of zaleplon, and its nocturnal use, would mitigate the clinical effects of any pharmacological interactions produced by its coadministration with other medications.

4.7 Sleep Architecture

Walsh et al.[32] noted a relative preservation of sleep architecture in terms of the percentage of total sleep time spent in each sleep stage with zaleplon 5mg and 10mg and triazolam 0.25mg over 2 weeks of treatment. Sleep architecture was likewise preserved during 5 weeks of treatment with zaleplon 10mg, aside from some minor changes in REM sleep in comparison with placebo.[36]

Stone et al.,[38] on a single night of recording, found a reduction in the duration (but not the percentage) of stage 1 sleep with middle-of-the night zaleplon 20mg. Zopiclone 7.5mg reduced the duration of stage 1 sleep and increased the duration of stage 3 sleep (and total sleep time). Drake et al.,[33] over 2 nights of recording, found significant in-

creases in stage 3/4 sleep with zaleplon 40mg and 60mg in comparison with placebo, whereas triazolam 0.25mg tended to decrease stage 3/4 sleep. Zaleplon 40mg and 60mg also reduced the percentage of REM stage sleep in comparison with placebo and significantly more so than triazolam 0.25mg. Sleep architecture with zaleplon 10mg and 20mg was well preserved in comparison with placebo.

Walsh et al.[39] found a dose-dependent increase in REM latency with zaleplon in older patients with insomnia over 2 nights of treatment. The REM latency with zaleplon 5mg was significantly greater than placebo in this population. Sleep architecture was otherwise well preserved with zaleplon 2mg, 5mg and 10mg.

4.8 Respiratory Depression

Caution is recommended when using benzodiazepines in the treatment of insomnia in patients with respiratory disorders such as chronic obstructive pulmonary disease (COPD) and obstructive sleep apnoea (OSA), owing to their potential to decrease respiratory effort, decrease upper airway muscle tone and blunt arousal responses to hypoxia/hypercapnia.[66] Little data exists with regard to the effect of zaleplon on respiratory function. George et al.[67] investigated the effects zaleplon 10mg, zolpidem 10mg and placebo over 3 consecutive nights in a group of 31 patients with insomnia and mild to moderate COPD. No significant differences from placebo were seen with either zaleplon 10mg or zolpidem 10mg on mean overnight SaO2, percentage of the night with SaO_2 <90% and the apnoea hypopnoea index (AHI). George[66] also reported data on the effects of zaleplon 10mg and zolpidem 10mg in 19 outpatients with mild to moderate OSA. Zaleplon 10mg was not associated with significant differences from placebo in the AHI, total duration of apnoea/hypopnoea episodes, mean SaO_2 and lowest SaO_2. Thus, although zaleplon appears to be safe in patients with mild to moderate COPD and OSA, further studies are clearly required.

4.9 Treatment Emergent Adverse Events

Beer et al.[24] noted a number of transient, neurologically related adverse events with zaleplon, primarily at a dose of 60mg, including drowsiness, dizziness, impaired concentration, impaired coordination and nystagmus, all of which were resolved within 1–2 hours.

Allen et al.[42] also reported that such neurological symptoms were common with zaleplon 20mg, but were less pronounced than with lorazepam 2mg. Interestingly, in this early study, the investigators reported that 4 of the 12 patients who received zaleplon 20mg experienced visual hallucinations (in comparison with 1 patient of 12 who received lorazepam 2mg). These hallucinations were described as being mild to moderate in intensity and consisting of objects in the room appearing to move, pulsate or spin. These disturbances were also of short duration, not unduly alarming and presumably of less significance in the sleeping patient. Bhatia et al.[68] have also reported a case of zaleplon-induced illusions and hallucinations.

Both Danjou et al.[50] and Hindmarch et al.[51] reported a similar incidence of adverse effects between zaleplon and placebo when given in the middle of the night, whereas zolpidem 10mg under the same conditions was associated with significantly more CNS adverse effects.

In long-term efficacy studies (2–5 weeks), the most commonly reported treatment emergent adverse effect with zaleplon was headache, but in general this was no more significant than placebo and neither were any other adverse effects.[32,34-36] Fry et al.[35] reported an increased overall treatment effect in the incidence of dizziness, which was particularly evident with zaleplon 20mg and zolpidem 10mg.

Beer et al.[24] did not note any changes in EEG activity at 6–8 hours and 24–25 hours post-dose. Greenblatt et al.[26] noted an increase in relative beta EEG activity with zaleplon 10mg and 20mg over 4 hours, but no more so than with zolpidem 20mg, which is consistent with its benzodiazepine agonist activity. In no study were significant effects report-

ed with zaleplon on vital signs, ECG, haematological and clinical chemistry parameters.

Hedner et al.[40] noted that in elderly patients with insomnia the most commonly reported adverse effects with zaleplon 5mg and 10mg were headache, pain and dizziness – none of which were reported significantly more often than with placebo. Likewise Ancoli-Israel et al.[41] found no significant differences in reported adverse effects from placebo in patients with insomnia receiving zaleplon 5mg and 10mg, in contrast to zolpidem 5mg, which produced a greater incidence of total CNS adverse effects, in particular somnolence.

5. Conclusion

Zaleplon has been shown in a number of studies to exhibit a benefit-risk profile consistent with its unique pharmacological profile, i.e. its ultra-short half-life and selective $GABA_A$ receptor binding. Zaleplon has been shown to be efficacious in promoting sleep initiation, but less so in promoting sleep maintenance. The adverse effects associated with zaleplon have been shown to be shorter in duration and/or lesser in magnitude than those associated with benzodiazepines (including triazolam) and longer acting non-benzodiazepine hypnotics (zolpidem and zopiclone). This improved risk profile includes the effects of zaleplon on psychomotor and cognitive performance, driving performance, tolerance, withdrawal and rebound, respiratory depression, sleep architecture and general adverse effects. More data is required with respect to its abuse potential and drug interactions (including alcohol).

It has often been said that the ideal hypnotic should be one with a rapid onset of action to promote sleep initiation, have a sustained effect to promote sleep maintenance and be free of next-day residual effects. No such hypnotic yet exists and clinicians are often left with the trade-off between maximising sleep duration and minimising next-day residual effects. Given the heterogeneity of insomnia, no singe medication should prove clearly superior. Zaleplon, with its ultra-short half-life, would appear to be particularly suited to patients with difficulties solely in initiating sleep or with isolated nocturnal awakenings (including early morning awakenings) and is uniquely suited for middle-of-the-night administration. Indeed it has been our clinical experience that zaleplon is particularly effective in this regard. Zaleplon may also be preferred by patients exposed to short sleep opportunities and unpredictable awakenings that require maximal alertness (e.g. military personal, physicians on call). The short duration of action may also be useful to shift workers wanting to undergo a second short sleep period before beginning work, but not wanting this 'nap' to be particularly long or associated with residual effects. Zaleplon, therefore, offers another option in the management of patients with insomnia.

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