

NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

Final Appraisal Determination

Zaleplon, zolpidem and zopiclone for the short-term management of insomnia

1 Guidance

- 1.1 When, after due consideration of the use of non-pharmacological measures, hypnotic drug therapy is considered appropriate for the management of severe insomnia interfering with normal daily life, it is recommended that hypnotics should be prescribed for short periods of time only, in strict accordance with their licensed indications.
- 1.2 It is recommended that, because of the lack of compelling evidence to distinguish between zaleplon, zolpidem, zopiclone or the shorter-acting benzodiazepine hypnotics, the drug with the lowest purchase cost (taking into account daily required dose and product price per dose) should be prescribed.
- 1.3 It is recommended that switching from one of these hypnotics to another should only occur if a patient experiences adverse effects considered to be directly related to a specific agent. These are the only circumstances in which the drugs with the higher acquisition costs are recommended.
- 1.4 Patients who have not responded to one of these hypnotic drugs should not be prescribed any of the others.

2 Clinical need and practice

- 2.1 Insomnia is a disturbance of normal sleep patterns commonly characterised by difficulty in initiating sleep (sleep onset latency) and/or difficulty maintaining sleep (sleep maintenance). However, insomnia is highly subjective and although most healthy adults typically sleep between 7 and 9 hours per night,

patterns vary greatly between people, and in any given person there are variations from night to night.

- 2.2 Insomnia can have a number of different causes: primary insomnia can be differentiated from insomnia associated with factors such as personal circumstances, physical or psychiatric co-morbidities, concomitant drug treatments or substance abuse (drugs, nicotine, alcohol or caffeine). A 1996 World Health Organization survey indicated that 52% of people reporting a sleep problem had a well-defined mental health disorder and 54% reported a physical disorder.
- 2.3 The published estimates of the prevalence of insomnia vary from 10–38%. This variation can be attributed to the epidemiology surveys utilising different definitions, classification systems and diagnostic criteria. A recent systematic review of the epidemiological literature suggested that, while 30–48% of people reported the presence of insomnia symptoms and 8–18% reported dissatisfaction with sleep quality or quantity, only 6% met the criteria for a diagnosis of insomnia. Although one in twenty people are believed to present to healthcare professionals with insomnia-related symptoms, it is thought that many people with insomnia do not seek medical help.
- 2.4 The prevalence of insomnia has been reported to be higher in women and to increase with age. The age-related increase is believed to be multifactorial in origin and has been associated with changes in the time spent in different stages of sleep, increasing co-morbidities, and lifestyle related factors.
- 2.5 Sleep disturbance and the resulting daytime fatigue cause distress and impairment of daytime functioning, both social and occupational, which have been associated with reduced quality of life. People with insomnia have been shown to have higher rates of mental health problems, drug and alcohol abuse, cardiac morbidity and healthcare utilisation, and to be at increased risk of accidents and overall mortality. However, it is difficult to differentiate the effects of insomnia from the effects of any associated factors, for example, co-morbidities.

- 2.6 The electrophysiological parameters of sleep can be objectively assessed using polysomnography (PSG), which monitors sleep architecture by using electrodes applied to the scalp. However, insomnia is very subjective and there is great variation in sleep parameters both between individuals and in individuals on different nights. Therefore, although objective data on sleep parameters (for example, time taken to get to sleep, duration of sleep and number of awakenings) can be collected, such data are difficult to interpret and do not fully capture the impact of the condition. More subjective evaluations can be made using generic and disease-specific quality of life instruments and self-report measures such as sleep diaries and sleep quality indices.
- 2.7 The choice of management strategy for insomnia is dependent upon both the duration and nature of the presenting symptoms. Appropriate management of existing co-morbidities may relieve the symptoms. The provision of advice on appropriate routines to encourage good sleep is fundamental to the overall management strategy, for example, avoiding stimulants and maintaining regular sleeping hours with a suitable environment for sleep. Other non-pharmacological interventions (for example, cognitive behavioural therapies) have also been shown to be effective in the management of persistent insomnia. However, although GPs and pharmacists can deliver appropriate advice and education, access to many non-pharmacological therapies is restricted through a combination of a lack of trained providers, cost and a poor understanding of available options.
- 2.8 A drug used to induce sleep is described as a 'hypnotic'. Although hypnotics can provide relief from the symptoms of insomnia, they do not treat any underlying cause. A number of hypnotic agents are licensed for the treatment of insomnia, including the benzodiazepines and zaleplon, zolpidem and zopiclone (Z-drugs).
- 2.9 It is difficult to ascertain how many prescriptions for hypnotics are written annually because benzodiazepines, which are commonly prescribed for

insomnia, are also prescribed for other conditions. Up to 40% of people with insomnia self-medicate with hypnotics that are available without prescription from pharmacies (for example, sedative antihistamines).

- 2.10 Benzodiazepines are a group of structurally related compounds that enhance the effects of gamma (γ)-aminobutyric acid (GABA), which is the major inhibitory neurotransmitter in the central nervous system. The *British National Formulary (BNF)* 46th edition lists six benzodiazepines (nitrazepam, flunitrazepam, flurazepam, loprazolam, lormetazepam and temazepam) in Section 4.1.1 on hypnotics. These agents are all available in generic form except for flunitrazepam and flurazepam, which are 'blacklisted' and cannot be prescribed within the NHS. A further two benzodiazepines, diazepam and lorazepam, are licensed for both insomnia and anxiety and are listed in the anxiolytic section of the *BNF* (Section 4.1.2).
- 2.11 The effects of specific benzodiazepines are dependent upon the dose administered and the pharmacokinetic profile. Although there is variation between the estimates of elimination half-life, the *BNF* refers to loprazolam, lorazepam, lormetazepam and temazepam as having a shorter duration of action. Benzodiazepines with a longer elimination half-life (for example, diazepam and nitrazepam) tend to have prolonged effects and, if used as hypnotics, have a greater tendency to have next-day residual effects. This may affect mental function and cause psychomotor impairment, which can interfere with activities such as driving and working with machinery.
- 2.12 One of the key concerns about the use of benzodiazepines is that many people develop tolerance to their effects, gain little therapeutic benefit from chronic consumption, become dependent on them (both physically and psychologically), and suffer a withdrawal syndrome when they stop taking them. The withdrawal syndrome may be prolonged and may develop at any time up to 3 weeks after cessation of a long-acting benzodiazepine, or a few hours after cessation of a short-acting one. The syndrome includes anxiety, depression, nausea and perceptual changes. 'Rebound insomnia' also occurs

and is characterised by a worsening of the original insomnia symptoms. There are also problems of abuse with benzodiazepines as they enhance and often prolong the 'high' obtained from other drugs and alleviate their withdrawal effects.

- 2.13 It has been estimated that 10–30% of chronic benzodiazepines users are physically dependent on them and 50% of all users suffer withdrawal symptoms. Factors potentially associated with an increased risk of developing dependency include short duration of action, long-term use, high dose, high potency, alcoholism and other drug dependency, personality disorders and use without medical supervision. The BNF notes that lorazepam is associated with a greater risk of withdrawal symptoms. The concerns over dependence led the Committee on Safety of Medicines to recommend that the use of benzodiazepines for the treatment of insomnia should be restricted to severe insomnia and that treatment should be at the lowest dose possible and not be continued beyond 4 weeks.

3 The technologies

- 3.1 Zaleplon, zolpidem and zopiclone (the Z-drugs) are non-benzodiazepine hypnotics. Although the Z-drugs differ structurally from the benzodiazepines, they are also agonists of the GABA receptor complex and therefore enhance GABA-mediated neuronal inhibition. The Z-drugs were developed with the aim of overcoming some of the disadvantages of benzodiazepines – for example, next day sedation, dependence and withdrawal.
- 3.2 Zaleplon is a pyrazolopyrimidine with an elimination half-life of 1 hour. It is licensed 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 patient to extreme distress. The Summary of Product Characteristics (SPC) specifies that treatment should be as short as possible with a maximum duration of 2 weeks.

- 3.3 Zolpidem is an imidazopyridine and has an elimination half-life of 2.5 hours. It is licensed for “the short-term treatment of insomnia in situations where the insomnia is debilitating or is causing severe distress for the patient”. The SPC states that the duration of treatment should usually vary from a few days to 2 weeks with a maximum of 4 weeks, including tapering off where appropriate.
- 3.4 Zopiclone is a cyclopyrrolone and has an elimination half-life of 3.5–6.5 hours. It is licensed for “the short-term treatment of insomnia (including difficulties in falling asleep, nocturnal awakening and early awakening, transient, situational or chronic insomnia, and insomnia secondary to psychiatric disturbances) in situations where the insomnia is debilitating or is causing severe distress for the patient”. The SPC states that long-term continuous use is not recommended, that a course of treatment should employ the lowest effective dose, and a single period of treatment should not exceed 4 weeks including any tapering off. The SPC also states that the duration of treatment should be 2–5 days for transient insomnia and 2–3 weeks for short-term insomnia.
- 3.5 In common with the benzodiazepines, the sedative effects of the Z-drugs may persist into the next day. The SPCs for all three Z-drugs carry warnings about their potential to cause tolerance, dependence and withdrawal symptoms. For full details of side effects and contraindications, see the SPCs.
- 3.6 The current acquisition costs for an adult dose are zaleplon (10 mg) £0.29, zolpidem (10mg) £0.16 and zopiclone (7.5 mg) £0.16 (excluding VAT; *BNF* 46th edition). Costs may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

The Appraisal Committee (Appendix A) considered evidence from a number of sources (see Appendix B). The remit given to NICE by the Department of Health/Welsh Assembly Government was to advise on the clinical and cost effectiveness of zaleplon, zolpidem and zopiclone relative to

benzodiazepines. The appraised evidence was therefore restricted to that informing comparison of the Z-drugs with benzodiazepines that are approved for the treatment of insomnia and may be prescribed within the NHS (diazepam, nitrazepam, loprazolam, lorazepam, lorazepam, lormetazepam and temazepam).

4.1 Clinical effectiveness

- 4.1.1 The Assessment Report reviewed data from 24 randomised controlled trials (RCTs) that compared the Z-drugs with either a benzodiazepine or with another Z-drug in patients with insomnia. In total, 11 different comparisons were made between benzodiazepines (temazepam, lormetazepam or nitrazepam) and zolpidem (4 RCTs) or zopiclone (13 RCTs). No RCTs were identified that compared zaleplon with a benzodiazepine. Six RCTs were reviewed that compared zaleplon with zolpidem and one that compared zolpidem with zopiclone.
- 4.1.2 The duration of the studies ranged from 1 night to 6 weeks. Ten studies included a follow-up period, which ranged from 3 to 11 days. The number of patients included in the trials ranged from 10 to 615. The most common comparator used in the RCTs was nitrazepam, which has a prolonged duration of action and may give rise to residual effects on the following day. None of the trials compared the Z-drugs against 10 mg temazepam or 1mg loprazolam. One of the ten studies used objective PSG recordings; the remaining nine collected data from post-sleep questionnaires and sleep diaries.
- 4.1.3 Five RCTs restricted their inclusion criteria to people of 60 years of age or older. Although it is recommended that the doses of both the Z-drugs and the benzodiazepine hypnotics should be reduced in older people, only three of the five RCTs used recommended doses for this age group. People over the age of 60 were amongst the population enrolled in a further 12 of the included RCTs. In these studies, standard dose hypnotics (benzodiazepines and Z-

drugs) were used with no reported dose reductions for the people over the age of 60.

- 4.1.4 The Assessment Group reported that it was difficult to compare the results of individual studies because of methodological problems and variations in the outcome measures used. In addition, direct statistical comparisons between the hypnotics included in individual RCTs were not always made, and often insufficient data were reported to permit further analysis. There was also evidence of multiple testing of outcomes, with selective reporting of significant findings.
- 4.1.5 Although in the individual RCTs there were some statistically significant differences between the Z-drugs and the benzodiazepines for some of the efficacy outcome measures, the differences were not consistent across the trials. In addition, in most cases the absolute difference was small and the clinical significance of the differences was difficult to ascertain. The Assessment Group concluded that there was no consistent pattern of superiority of one drug over another.
- 4.1.6 Six RCTs compared zaleplon with zolpidem. One RCT found that 10 mg zaleplon per night resulted in statistically significant shorter sleep onset latency than 5 mg zolpidem (median time 31 minutes versus 42 minutes). Pooled data from three RCTs indicated the sleep was of less quality (odds ratio [OR] 0.66; 95% confidence interval [CI]: 0.51 to 0.87) and the median sleep time was statistically significantly less with 5 mg zaleplon per night compared with 5 mg zopiclone (291 minutes versus 309 minutes). Compared with 7.5 mg zopiclone, 10 mg zolpidem per night was associated with shorter sleep onset latency (OR 1.72; 95% CI: 1.04 to 2.84) in the 2-week trial identified. In the cross-over study, there were no statistically significant differences between 10 mg zaleplon and 10 mg zolpidem in the patients' global impression of treatment (38% versus 62%).
- 4.1.7 There was little consistency in the reporting of adverse events, which prevented comparison of individual event rates or meta-analysis. There were

no statistically significant differences in the rates of treatment-emergent adverse events associated with any of the comparisons of Z-drugs versus benzodiazepines. There were no consistent differences between the Z-drugs and the benzodiazepines in the incidence of next-day residual effects.

4.1.8 In the RCT comparisons between the Z-drugs and benzodiazepines in people with insomnia, no data were identified on the frequencies of symptoms associated with withdrawal or dependency. In their submissions, the manufacturers also referenced a number of other studies that examined the rates of tolerance and dependency associated with the Z-drugs. The studies were not considered to be methodologically robust and there were no direct comparisons between the Z-drugs and the benzodiazepines used in the NHS.

4.1.9 The Assessment Group also searched for studies of other designs that specifically evaluated rates of dependence and withdrawal symptoms following treatment with the Z-drugs. Six studies were identified, four of which evaluated patients after extended treatment periods. Two placebo-controlled studies examined relative rates of withdrawal symptoms after patients receiving zolpidem were switched to placebo after 3 or 4 weeks of treatment. In one study, no patient in either group reported more than one symptom after 4 weeks treatment with 10 mg zolpidem or placebo and in the second study, three older patients who had received zolpidem at doses of 10–20 mg experienced adverse events. In addition, information on cases of dependence reported to the Committee on Safety of Medicines was sought and 16 case reports were identified in the literature relating to zolpidem (11) and zopiclone (5). There are problems with the interpretation of such reports, as rates of reporting are dependent on the publicity and awareness of certain adverse reactions and the pattern of use of the drugs.

4.1.10 In addition to the RCTs conducted in people with insomnia, a further 9 RCTs, which were conducted in healthy volunteers in whom insomnia had been induced, were submitted by the manufacturers. Most of these 9 studies had very small sample sizes (less than 30 people) or were of very short duration

(for example 1–3 nights). The largest study was conducted in 630 people and compared 10 mg zolpidem with 15 mg temazepam, 0.25 mg triazolam or placebo. Data were collected from multiple outcome measures. There were no statistically significant differences between zolpidem and temazepam in objective measures of sleep latency and sleep efficiency. The zolpidem group had statistically significantly fewer awakenings than the temazepam group. For the subjective measures, the group receiving zolpidem reported greater ease in falling asleep, more sleep time and less wake time than those receiving temazepam. There were no statistically significant differences in subjects' ratings of their ability to concentrate or morning sleepiness.

4.1.11 A manufacturer submitted evidence from two RCTs that compared continuous zolpidem use (10 mg per night) with intermittent use. Data for each night were not reported but the submission reported that there were no statistically significant differences in the sleep efficacy outcomes, other than the investigators assessment of sleep onset latency, which was statistically significantly greater in the continuous zolpidem group. No similar studies were located for zaleplon, zopiclone or any benzodiazepine.

4.1.12 In summary, the Assessment Group did not find any RCTs that appropriately compared the Z-drugs with shorter-acting benzodiazepines, used at appropriate doses. In the RCTs that were reviewed by the Committee, which had been conducted in both healthy volunteers and people with insomnia, there were no consistent differences between the drugs. However, this lack of consistency was attributed in part to the poor quality of reporting.

4.2 Cost effectiveness

4.2.1 None of the submissions contained an economic evaluation that compared the costs and effects of the short-term use of Z-drugs with benzodiazepines. In addition, the Assessment Group was unable to identify any evaluations in the health economics literature. No comparative data on the health-related quality of life associated with Z-drugs and benzodiazepines using generic

health status measures were identified, and there was no evidence to link the clinical end-points from the trials with quality of life.

4.2.2 The manufacturer of zaleplon submitted two models based upon the key assumption that zaleplon does not cause 'mental impairment' the day after administration.

4.2.2.1 The first model consisted of a cost–consequence algorithm comparing the costs and additional road traffic accidents (RTAs) associated with the residual effects of zopiclone and zaleplon. This model was based on a study mapping residual effects of zopiclone and zaleplon to RTAs using data from three other studies. The first stage of the mapping procedure was to estimate the impact of the residual effects of the Z-drugs on driving performance. This was taken from a double-blind study of 28 healthy volunteers given zaleplon, zopiclone or placebo in the evening. The volunteers were woken in the middle of the night and given either placebo (those who had earlier taken active medication) or zaleplon, zopiclone or placebo (those who had earlier taken placebo). Participants undertook a series of tests, including a driving performance test, the following morning. . The results found that driving performance was statistically significantly worse in the zopiclone group, and performance after zaleplon was similar to that for placebo. These results were linked to data from a similar study designed to measure the driving performance associated with differing levels of blood alcohol content. The relationship between blood alcohol content and the residual effects of the Z-drugs was then estimated. The relationship between relative risk of RTAs and blood alcohol content was estimated using data from a case–control study. The results of the model suggest that the expected excess accident costs, combined with drug purchase costs, over a 2-week period were US\$71 per person for 10 mg zaleplon and US\$92 per person for 10 mg zopiclone.

4.2.2.2 In support of the economic model, the manufacturer of zaleplon also cited a UK-based study which examined a sample of drivers involved in RTAs and

compared the odds of having an accident whilst exposed or not exposed to specified drugs. The study found that zopiclone and anxiolytic benzodiazepines, but not hypnotic benzodiazepines, were associated with increased risk of RTAs. The manufacturer also cited a Canadian study estimating the relationship between hypnotic drugs and RTAs in older people. The study found that benzodiazepines with a long half-life were associated with an increased risk of RTAs, but that those with a short-half life were not. Concern was expressed regarding this study at the time of publication, particularly with regard to the failure to adequately control for confounding effects and the lack of distinction between benzodiazepines used as hypnotics and those used as anxiolytics.

4.2.2.3 The manufacturer of zaleplon also submitted a model designed to estimate the costs associated with hip fractures caused by falls as a result of the residual effects of zolpidem, nitrazepam, temazepam and zaleplon. The model assumed treatment on a basis of 2 weeks on therapy followed by 2 weeks off therapy over a one-year period and did not take into account benefits relating to treatment. This model was based on a published retrospective study, which examined the use of sedative hypnotics using Medicare data in a sample of older patients. Each case, defined as a patient who underwent surgical care for hip fracture, was matched by four age–gender matched controls from the Medicare database. Confounding factors are likely to bias results in studies of this type, particularly as insomnia may be a result of co-morbid conditions, which in turn could increase the risk of falls. Attempts to reduce confounding were made by adjusting crude odds ratios by a number of factors, including a measure of co-morbid illness severity. The study found that zolpidem use and benzodiazepine use were associated with a statistically significant increase in the risk of hip fracture. The model used the adjusted odds ratios from this study to represent the increased risk of hip fracture. The manufacturer assumed no additional risk of hip fracture was associated with zaleplon (that is, adjusted OR 1.0), although this drug had not been evaluated in the published study. The

results of the model suggest that per year zolpidem, nitrazepam and temazepam therapy were more expensive than zaleplon when treating a cohort of 10,000 patients by £821,000, £129,000 and £111,000, respectively.

- 4.2.3 The Assessment Group reanalysed the hip fractures model after correcting some errors and adding illustrative quality-adjusted life year (QALY) values, but retaining the key assumption that zaleplon was not associated with increased risk of hip fractures. The Assessment Group concluded from the results of the amended model that at current acquisition costs, after taking into account the uncertainty surrounding all of the model inputs, the drugs included in the analysis appeared similarly cost effective compared with no treatment.
- 4.2.4 A manufacturer of zolpidem submitted a discussion of a model to estimate the costs of long-term zolpidem treatment compared with temazepam treatment. The model used estimates of dependence based on national prescribing data and concluded that despite having higher costs per dependent and non-dependent patient, zolpidem was shown to cost less on average because of its lower likelihood of high-cost dependency. However, the manufacturer stated that, “in the absence of robust data on the incidence of dependence, the author had to rely on a weak surrogate indicator of dependence in the form of continuous use”.
- 4.2.5 In summary, the manufacturers suggest that the additional acquisition costs of Z-drugs would be offset by reduced consumption of other healthcare resources or lead to an improvement in health outcomes as a result of decreased dependence or reduced residual effects.

4.3 Consideration of the evidence

- 4.3.1 The Committee reviewed the evidence available on the clinical and cost effectiveness of zaleplon, zolpidem and zopiclone, having considered evidence on the nature of the condition and the value placed by users on the

benefits of zaleplon, zolpidem and zopiclone from people with insomnia, those who represent them, and clinical experts. It was also mindful of the need to take account of the effective use of NHS resources.

- 4.3.2 The Committee heard testimony that insomnia is generally not well managed and that there is a lack of availability of training for healthcare providers in this field. It was advised that, despite national recommendations and restrictions specified in the SPCs, hypnotic agents are commonly used for minor degrees of insomnia and also prescribed for long periods. Use of these agents for extended periods is associated with increased likelihood of dependence.
- 4.3.3 The Committee heard evidence that some non-pharmacological strategies, including simple techniques such as the provision of advice on appropriate routines to encourage good sleep, (for example, avoiding stimulants and maintaining regular sleeping hours with a suitable environment for sleep) had been shown to be effective in the management of insomnia. The Committee considered that it was likely that such strategies could replace some of the current prescribing of hypnotics. However, non-pharmacological therapies did not fall within the remit of this appraisal and therefore their clinical and cost effectiveness had not been determined.
- 4.3.4 The Committee appreciated that there were differences in the pharmacokinetics of the individual hypnotics (both Z-drugs and benzodiazepines) which may have some benefits in specific clinical situations. For example, a hypnotic that is rapidly absorbed and rapidly cleared will inevitably result in shorter sleep onset latency, but it may not extend the total sleep duration as its effects will rapidly wear off. The Committee was not however persuaded that these differences resulted in any overall benefit for the majority of patients in terms of perceived quality of sleep, daytime functioning or quality of life. The Committee were also aware that when comparing the Z-drugs to nitrazepam and diazepam, consideration needed to be given to the fact that it was inevitable that the longer-half life of these

benzodiazepines would be associated with an increased likelihood of persistence of the sedative effects into the next day.

4.3.5 The Committee considered that the RCTs available, in both people with insomnia and healthy volunteers, did not reflect current NHS practice: none of the Z-drugs had been compared with appropriate hypnotic doses of temazepam and the most common comparator used in the RCTs was nitrazepam, which has a prolonged duration of action and may give rise to residual effects on the following day. The Committee also appreciated that the effects of both the Z-drugs and the benzodiazepines were dose-related and that inappropriate comparisons, particularly in older people, would confound the results of the RCTs.

4.3.6 The Committee was made aware by the patient organisation that warnings regarding potential dependence associated with extended use of hypnotics are often not passed to patients. The Committee was particularly concerned that patients may be preferentially prescribed Z-drugs or transferred from benzodiazepines to the Z-drugs because of a perception that they are less likely to induce dependency than the benzodiazepines. In addition, the Committee considered that the substitution of the Z-drugs for patients who were being withdrawn from benzodiazepines was inappropriate and not supported by available evidence of reduced potential for dependency.

4.3.7 The Committee recognised that the benzodiazepines are abused and was informed by both the experts and the patient representatives that, although there was limited epidemiological evidence, abuse of the Z-drugs was increasing.

4.3.8 Having considered the results of the RCTs and healthy volunteer studies, together with the testimony from the professional and patient experts, the Committee concluded that currently there was no compelling evidence of a clinically useful difference between the Z-drugs and shorter-acting benzodiazepine hypnotics from the point of view of their effectiveness, adverse effects, or potential for dependence or abuse. There was no

evidence to suggest that if a patient did not respond to one of these hypnotic drugs, they were likely to respond to another and this was supported by testimony from the clinical and patient experts. The Committee therefore concluded that 'switching' between these hypnotics was not an appropriate management strategy.

4.3.9 The Committee considered the economic models submitted by one of the manufacturers. The Committee fully discussed the basis of the manufacturer's models and recognised that they were based on the premise that the use of individual Z-drugs in preference to other Z-drugs or benzodiazepines would prevent road traffic accidents or hip fractures caused by falls. The Committee did not accept these models as it considered that the evidence used in them was not robust and the additional assumptions underpinning the models were not appropriate. In addition, the Committee considered that there was no reliable evidence to support the claim that the higher acquisition costs of the Z-drugs would be offset by the reductions in the use of other health service resources.

4.3.10 In summary, given the lack of compelling evidence on any clinically useful differences between the Z-drugs and the shorter-acting benzodiazepine hypnotics, the Committee concluded that, unless a patient experiences adverse effects considered to be directly related to a specific hypnotic, the drug with the lowest purchase cost (taking into account daily required dose and product price per dose) should be used in preference to more expensive alternatives.

5 Recommendations for further research

5.1 Although RCTs to assess the relative clinical effectiveness, and cost effectiveness of the Z-drugs and the shorter-acting benzodiazepines could potentially clarify some of the uncertainty, it is unlikely that they would be a cost-effective use of NHS resources. Efforts should therefore be concentrated on determining the clinical and cost effectiveness of pharmacological

treatments relative to non-pharmacological interventions, including their relative roles in the long-term management of insomnia.

- 5.2 Previous trials have concentrated on the use of sleep-specific measures of outcomes, which have not been directly related to improvements in daytime functioning and quality of life. Further research should therefore include the impact of hypnotics and any resultant improvement in sleep quality, on daytime functioning and health-related quality of life.
- 5.3 There is limited evidence on the risk of dependency associated with the Z-drugs and benzodiazepines. In particular, the risk of dependence should be examined with respect to intermittent use of hypnotics, and the relationship between risk of dependence and length of treatment.
- 5.4 The patient groups informed the Committee that there was a lack of support for patients and inadequate information about the management of insomnia and the risks associated with the use of hypnotics. Research should therefore be conducted to establish the most suitable method of conveying good quality information to people with insomnia.

6 Implications for the NHS

- 6.1 It is likely that this guidance will result in the preferential prescription of hypnotics with lower acquisition costs and possibly lead to a reduction in the prescribing of hypnotics, both overall and more specifically for long-term use. It is therefore expected that there will be some savings in terms of costs directly associated with the prescription of hypnotics. In 2002, a total of 3.9 million prescriptions were written for Z-drugs with a net ingredient cost of £15.9 million. However, the overall effect and the timescale of this effect on NHS resources will depend on any reduction in overall hypnotic prescribing, the proportion of prescriptions relating to the short-term management, the proportion of patients prescribed more expensive hypnotics as a result of adverse effects directly related to the cheaper alternatives and the uptake of any non-pharmacological alternatives.

7 Implementation and audit

- 7.1 NHS organisations and clinicians who prescribe treatment for people with insomnia should review their current practice and policies and the current patterns of prescribing hypnotic drugs, as reported in high-level performance indicators, to take account of the guidance set out in Section 1.
- 7.2 Local guidelines, protocols or care pathways that refer to the care of people with insomnia should incorporate the guidance in Section 1.
- 7.3 To measure compliance locally with the guidance, the following criteria could be used. Further details on suggestions for audit are presented in Appendix C.
- 7.3.1 Hypnotic drug therapy is used for the management of severe insomnia interfering with normal daily life only after due consideration of the use of non-pharmacological measures.
- 7.3.2 When hypnotic drug therapy is used, the drugs are prescribed for short periods of time only, in strict accordance with the licensed indications.
- 7.3.3 When hypnotic drug therapy with shorter-acting benzodiazepine hypnotics, zaleplon, zolpidem or zopiclone, is prescribed, the drug with the lowest purchase cost is chosen.
- 7.3.4 A patient is switched from one of these hypnotic drugs to another only if he or she experiences adverse effects considered to be directly related to a specific agent.
- 7.3.5 A patient who has not responded to one of these hypnotic drugs is not prescribed any of the others.

8 Related guidance

- 8.1 There is no specific related NICE guidance for the management of insomnia.

9 Review of guidance

- 9.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider any new evidence on the technology, in the form of an updated Assessment Report, and decide whether the technology should be referred to the Appraisal Committee for review.
- 9.2 The guidance on this technology will be reviewed in December 2006.

Andrew Dillon
Chief Executive
January 2004

Appendix A. Appraisal Committee members

NOTE The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets twice a month except in December, when there are no meetings. The Committee membership is split into two branches, with the chair, vice-chair and a number of other members attending meetings of both branches. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr A E Ades

Senior Scientist, MRC Health Services Research Collaboration, University of Bristol

Professor Ron Akehurst

Dean, School of Health Related Research, University of Sheffield

Dr Tom Aslan

General Practitioner, Stockwell, London

Professor David Barnett (Chair)

Professor of Clinical Pharmacology, University of Leicester

Professor Sheila Bird

MRC Biostatistics Unit, Cambridge

Dr Karl Claxton

Health Economist, University of York

Dr Richard Cookson

Senior Lecturer, Health Economics, School of Health Policy and Practice, University of East Anglia, Norwich

Professor Gary A Ford

Professor of Pharmacology of Old Age/Consultant Physician, Newcastle upon Tyne Hospitals NHS Trust

Ms Bethan George

Interface Liaison Pharmacist, Tower Hamlets PCT and Royal London Hospital, Whitechapel

Dr Trevor Gibbs

Head, Global Clinical Safety & Pharmacovigilance, GlaxoSmithKline, Greenford

Mr John Goulston

Director of Finance, Barts and the London NHS Trust

Professor Robert Kerwin

Professor of Psychiatry and Clinical Pharmacology, Institute of Psychiatry, London

Professor Philip Home

Professor of Diabetes Medicine, University of Newcastle upon Tyne

Dr Terry John

General Practitioner, The Firs, London

Mr Muntzer Mughal

Consultant Surgeon, Lancashire Teaching Hospitals NHS Trust, Chorley

James Partridge

Mrs Kathryn Roberts

Nurse Practitioner, Hyde, Cheshire

Professor Philip Routledge

Professor of Clinical Pharmacology, College of Medicine, University of Wales, Cardiff

Ms Anne Smith

Lay Representative; Trustee, Long-Term Medical Conditions Alliance

Professor Andrew Stevens (Vice-Chair)

Professor of Public Health, University of Birmingham

Dr Cathryn Thomas

General Practitioner, and Senior Lecturer, Department of Primary Care & General Practice, University of Birmingham

Dr Norman Vetter

Reader, Department of Epidemiology, Statistics and Public Health, College of Medicine, University of Wales, Cardiff

Dr David Winfield

Consultant Haematologist, Royal Hallamshire Hospital, Sheffield

A. NICE Project Team

Each appraisal of a technology is assigned to a Health Technology Analyst and a Technology Appraisal Project Manager within the Institute.

Sarah Garner

Technical Lead, NICE project team

Louise Longworth

Technical Lead, NICE project team

Joanna Richardson

Technical Lead, NICE project team

Kathleen Dalby

Project Manager, NICE project team

Appendix B. Sources of evidence considered by the Committee

A The assessment report for this appraisal was prepared by the Liverpool Reviews and Implementation Group.

Newer hypnotic drugs for the management of insomnia, August 2003

B The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD). Consultee organisations are provided with the opportunity to appeal against the Final Appraisal Determination.

I Manufacturer/sponsors:

- Aventis
- Generics (UK)
- Lagap Pharmaceuticals
- Pliva Pharma
- Sanofi Synthelabo
- Wyeth

II Professional/specialist and patient/carer groups:

- Age Concern Cymru
- Age Concern England
- British Association for Service to the Elderly
- British Geriatrics Society
- British Sleep Society
- Council for Involuntary Tranquilliser Addiction
- Royal College of General Practitioners
- Royal College of Psychiatrists
- Royal Pharmaceutical Society of Great Britain

- Royal Society of Medicine, Sleep Medicine Section
- Sleep Matters, Medical Advisory Service

III Other groups:

- Department of Health
- Kingston Primary Care Trust
- Welsh Assembly Government

IV Commentator organisations (without the right of appeal):

- British National Formulary (BNF)
- Loughborough Sleep Research Centre
- NHS Confederation
- NHS Quality Improvement Scotland
- Sleep Assessment and Advisory Service
- Sleep Research Centre, University of Glasgow

C The following individuals were selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on zaleplon, zolpidem and zopiclone for the management of short-term insomnia by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Ms Pam Armstrong, Clinical Nurse Specialist & Advisor, Council for Involuntary Tranquilliser Addiction
- Professor Heather Ashton, Emeritus Professor of Clinical Psychopharmacology, Division of Psychiatry, University of Newcastle upon Tyne
- Mrs Helen Kay, on behalf of Council for Involuntary Tranquilliser Addiction

- Dr Adrian Williams, Consultant Physician and Director, Sleep Disorders Centre, St Thomas' Hospital, London
- Professor Kevin Morgan, Professor of Gerontology, Sleep Research Centre, Loughborough University

Appendix C. Detail on criteria for audit of the use of zaleplon, zolpidem and zopiclone for the short-term management of insomnia

Possible objectives for an audit

An audit could be carried out on the appropriateness of use of zaleplon, zolpidem and zopiclone.

Possible patients to be included in the audit

An audit could be carried out on all patients treated for insomnia for a suitable time period for audit, for example, 3–6 months.

Alternatively, an audit could be carried out over a suitable time period, for example, 3–6 months, on all patients for whom hypnotic drug therapy is prescribed.

Measures that could be used as a basis for an audit

The measures that could be used in an audit of zaleplon, zolpidem and zopiclone for the management of insomnia are as follows.

Criterion	Standard	Exception	Definition of terms
1. Non-pharmacological measures are considered before the prescription of drug therapy for insomnia	100% of patients being treated for insomnia	None	For audit purposes, clinicians will need to agree locally on how non-pharmacological measures are defined and how consideration of their use is documented.
2. When hypnotic drug therapy is used, the drug used is prescribed for a short period of time only, in strict accordance with the licensed indications	100% of patients for whom hypnotic drug therapy is prescribed	None	Drug therapy for insomnia can include zaleplon, zolpidem, zopiclone or the shorter-acting benzodiazepine hypnotics (loprazolam, lormetazepam and temazepam).. For audit purposes, clinicians will need to agree locally on how to define the duration of a prescription. The maximum duration of a prescription for zaleplon is 2 weeks and for zolpidem and zopiclone is 4

			weeks. Also for audit purposes, clinicians will need to agree locally on how to define and measure the consistency of prescriptions with licensed indications for each drug.
3. When hypnotic drug therapy is prescribed, the drug with the lowest purchase cost is chosen	100% of patients for whom hypnotic drug therapy is prescribed	A. The patient experiences adverse effects considered to be directly related to the first-line choice	The lowest purchase cost takes into account the daily required dose and the product price per dose. For audit purposes, clinicians will need to agree locally on the source of cost information and on how adverse effects of a specific drug are documented.
4. A patient is switched from one hypnotic drug to another	0% of patients for whom hypnotic drug therapy is prescribed	A. The patient experiences adverse effects considered to be directly related to a specific agent	Clinicians will need to agree locally on how adverse effects of a specific drug are documented for audit purposes.

An audit on all patients for whom hypnotic drug therapy is prescribed could be carried out using the measures above.

Calculation of compliance

Compliance (%) with each measure described in the table above is calculated as follows.

$$\frac{\text{Number of patients whose care is consistent with the **criteria** plus number of patients who meet any **exception** listed}{\text{Number of patients to whom the **measure** applies}} \times 100$$

Clinicians should review the findings of measurement, identify whether practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that the desired improvement is being achieved.