

Indiplon in the treatment of sleep disorders

Alan Lankford

Sleep Disorders Center of Georgia,
Atlanta, GA, USA

Abstract: Indiplon is a novel sedative-hypnotic recently approved for the treatment of insomnia. Like other non-benzodiazepine hypnotics, its mechanism of action is to modulate subunits, especially the alpha-1 subunit, of the GABA receptor complex in order to induce sedation. Indiplon was developed in two different formulations to address two different types of insomnia complaint: indiplon-IR (immediate release) was designed for sleep onset difficulties, while indiplon-MR (modified release) was developed for sleep maintenance insomnia. While there are currently few peer reviewed articles about indiplon clinical trial results, the early information that is available seems to indicate that both formulations have been well tolerated and have proven effective at improving both patient reported and objectively measured sleep parameters in both adult and elderly insomnia patients. In May 2006, the FDA indicated that indiplon-IR was approvable and plans are to resubmit the application in 2007. Indiplon-MR was unapprovable and may require further evaluation.

Keywords: indiplon, insomnia, GABA_A receptor, sedative, non-benzodiazepine

Introduction

Insomnia is a common sleep disorder with potentially serious economic, health and quality of life ramifications if left untreated. It is characterized by symptoms of difficulty falling asleep, difficulty staying asleep, waking too early or poor quality or non-restorative sleep (American Psychiatric Association 2000; American Sleep Disorders Association 2001). Epidemiological studies have documented the prevalence of chronic insomnia in 10%–15% of the general population (Ford and Kamerow 1989; Ancoli-Israel and Roth 1999; National Sleep Foundation 2002, 2003, 2004, 2005; Drake et al 2003). Furthermore, as many as half of all Americans experience transient episodes of insomnia symptoms due to acute circumstances (National Sleep Foundation 2002, 2003, 2004, 2005).

Chronic insomnia is associated with significant daytime distress. Consequences of the disease can include functional impairment, increased risk of accidents and reductions in quality of life (Ford and Kamerow 1989; Balter and Uhlenhuth 1991; Rosenthal et al 1993; Zammit 1999). Specific medical conditions associated with insomnia include coronary artery disease, hypertension and musculoskeletal problems (Gislason et al 1993; Janson et al 2001; Mallon et al 2002). Additionally, numerous studies have established a remarkably high association between insomnia and psychiatric disorders, especially depression, other affective disorders and anxiety (Ford and Kamerow 1989; Benca et al 2004). Evidence of a bidirectional interaction between insomnia and other co-morbidities, specifically depression and some pain disorders is beginning to emerge (Moldofsky et al 1975; Moldofsky and Scarisbrick 1976). Across several studies lasting up to 35 years, insomnia has been shown to increase the risk for the development of depression by as much as a factor 5 (Ford 1989; Breslau 1996). Meanwhile, pain has been shown to exacerbate sleep difficulties, while poor sleep intensifies the perception of pain (Moldofsky et al 1975; Moldofsky and Scarisbrick 1976; Drewes et al 1997).

Correspondence: Alan Lankford
5505 Peachtree Dunwoody Road,
Suite 380, Atlanta, GA 30342, USA
Tel +1 404 257 0080
Fax +1 404 257 0592
Email alankford@sleepsciences.com

While the underlying causes of insomnia are only partially understood, certain risk factors may predispose individuals to this disorder. These risk factors include age, gender, psychiatric or physical illness, the use of stimulants like caffeine and nicotine, some forms of shift work and poor sleep hygiene. Other potential contributors, including genetic etiology, are the focus of on-going research.

Recently, the serious consequences of insomnia have begun to receive more prominent attention. After a hiatus of 22 years, the National Institutes of Health convened a State of the Science conference on chronic insomnia in mid-2005 (National Institutes of Health 2005). Notably, the conference statement recommended that insomnia be considered as either a primary disorder or co-morbid with other disorders. Prior to this assertion, insomnia was typically considered to be a symptom secondary to other medical conditions and, as such, was often undertreated. Furthermore in the past few years, several new drugs were approved by the FDA for the treatment of insomnia. Greater national attention to the disorder and an expanded number of treatment options have resulted in marked changes in the pharmaceutical marketplace. Sales of prescription sleep aids in the U.S. have markedly increased from approximately \$900M in 2000 to more than \$2.1B in 2004 (Iskowitz 2005).

Most of the currently available hypnotics are best suited to address difficulties with sleep onset (eg, difficulty falling asleep). Two of the newest treatment options, eszopiclone and zolpidem-CR, appear to assist patients with sleep maintenance difficulties (eg, nighttime awakenings). In order to minimize the potential for negative events associated with residual daytime sedation, all currently approved insomnia therapies are recommended to be taken prior to bedtime so that a patient can spend a full 8 hours in bed. As information about the health impact of insomnia is more widely disseminated and physicians continue to place more importance on its treatment, the number of patients taking prescription sleep medicine will continue to grow, as will the need for more specialized treatment options.

Current treatment options

Benzodiazepines were among the first modern drugs developed to treat the symptoms of insomnia. Benzodiazepines specifically approved for this purpose included flurazepam (Dalmane), temazepam (Restoril), triazolam (Halcion), quazepam (Doral) and estazolam (Prosom) (Eddy and Walbroehl 1999). This class of drug targets the GABA receptors and can produce sedative, hypnotic, anxiolytic, anticonvulsive, anesthetic and muscle-relaxant effects (Haefely et al 1992).

Unfortunately, most benzodiazepines interact with the entire GABA receptor complex, creating several of these effects simultaneously. Furthermore, short term use of benzodiazepines is recommended because of concerns about tolerance, dependence and the potential for significant adverse events (Kales et al 1983; Bixler et al 1987; Adams and Oswald 1989; Holbrook et al 2000).

More recently, treatment options have grown to include non-benzodiazepines and melatonin agonists. The off-label usage of other drug classes (eg, antidepressants, antihistamines) to treat insomnia complaints is also common, although there is limited evidence that these agents are safe and effective for use in this manner (Hartmann 1995; Nowell et al 1999; Richardson et al 2002).

In contrast to the benzodiazepines, the non-benzodiazepines are more selective for specific GABA receptor subunits associated with sedation. These compounds have a rapid onset of action and also rapidly eliminated from the body. Thus, they are able to quickly induce sedation with fewer of the next-day effects associated with some longer acting benzodiazepines (Nicholson et al 1983; Walsh et al 1990; Scharf et al 1994; Walsh et al 1998; Fry et al 2000). Non-benzodiazepines approved for the U.S. market include: zaleplon, zolpidem, zolpidem-CR and eszopiclone, the S-isomer of zopiclone. Zopiclone is widely used as a sedative outside the U.S.

At present, ramelteon is the only melatonin agonist approved for insomnia therapy. It acts on the MT_1 and MT_2 receptors which help maintain the circadian rhythms underlying the normal sleep-wake cycle (Brzezinski 1997; Hirai et al 2003). An important difference between ramelteon and both the benzodiazepines and non-benzodiazepines is that it has not been designated as a scheduled drug by the U.S. Drug Enforcement Agency due to its clinically established, extremely low potential for abuse (Hirai et al 2005; Griffiths et al 2005; France et al 2006). In addition, ramelteon is a completely different way to treat insomnia medically, focusing on the melatonin pathway rather than the GABA pathway.

Indiplon is one of the newest insomnia treatments in the non-benzodiazepine class. In contrast to other members of this class, two formulations of indiplon were simultaneously developed in order to address two distinct insomnia complaints. Indiplon-IR (immediate release) was designed to address sleep onset difficulties, both at the beginning of the night and after middle of the night awakenings. Indiplon-MR (modified release) was designed to address sleep maintenance difficulties. The FDA gave Neurocrine Biosciences an approvable letter for Indiplon-IR in May 2006

and simultaneously stated that the approval of Indiplon-MR would require further discussions and potentially additional development efforts.

Pharmacology of indiplon

Indiplon is a novel pyrazolopyrimidine with the empiric formula $C_{20}H_{16}N_4O_2S$. It is chemically described as *N*-Methyl-*N*-[3-[3-(thien-2-ylcarbonyl)pyrazolo[1,5 α]pyrimidin-7-yl]phenyl]acetamide.

Indiplon pharmacokinetics (PK) have been investigated in both animal and human studies. Healthy young male and female humans have demonstrated a maximal concentration (C_{max}) of indiplon at 0.73 and 0.82 hours after dosing and exhibited an elimination half life ($t_{1/2}$) of 1.97 and 1.71 hours, respectively (Rogowski et al 2002). Even though slight gender differences were observed, they were not statistically significant. Another study comparing indiplon PK in healthy adult and elderly subjects found that indiplon's peak plasma concentration was reached in 2.3 hours and the elimination half life was 1.5 hours in the younger group, as compared to 2.7 hours and 1.8 hours in the older group (Jochelson et al 2002). Again, these differences did not prove to be statistically significant.

Differences in PK values due to gender and age are frequently observed with both other hypnotics. Maximum concentration, total exposure and half life can be up to 50% greater in women (Rosen et al 1999; Greenblatt et al 2000). In the elderly, impaired renal and hepatic function can lead to a 3-fold increase in plasma concentrations and a doubling of half-life relative to the values seen younger adults. PK differences due to gender have been associated with metabolization via the hepatic isoform CYP 3A4, while age differences have been linked to the cytochrome P450 metabolic pathway (Greenblatt et al 1991, 2000). Indiplon is metabolized equally by CYP 3A4 and non-microsomal esterases, potentially explaining its relative lack of gender and age effects as compared to other hypnotics.

Of the currently available treatments, zaleplon is the only non-benzodiazepine hypnotic of the pyrazolopyrimidine class, the same chemical class as indiplon. Compared to indiplon, zaleplon has a somewhat shorter time to peak plasma concentration at approximately one hour as well as a shorter elimination half life of approximately one hour. The pharmacokinetics of zaleplon do not vary significantly with age or gender, however hepatic impairment can lead to a 4–7-fold increase in plasma concentration, a finding similar to indiplon.

While indiplon has not been shown to interact with alcohol, zaleplon potentiates the CNS-impairing effects for 1–2.5 hours after co-administration. Finally, zaleplon, like indiplon, shows no development of tolerance during short term nightly administration.

A significant difference between these two compounds is that indiplon is 10 times more selective for the GABA-A alpha 1 subunit, which is associated with sedation, compared to the alpha 2, 3 or 5 subunits. Zaleplon is only twice as selective for the alpha 1 subunit.

Co-administration of indiplon and alcohol does not have been shown to produce any pharmacokinetic or pharmacodynamic (PD) interactions (Berkowitz et al 2003). The absence of effect on PK values is expected since alcohol and indiplon are eliminated via different metabolic pathways. However, the absence of impact on PD parameters is noteworthy and unique relative to many other hypnotics.

Finally, the potential for indiplon to produce tolerance was evaluated in healthy volunteers (Jochelson, Chen et al 2003). Both PK and PD parameters were essentially unchanged between the first and last day of the two week study at all dose levels (10–40 mg), indicating no development of tolerance following repeat administration of indiplon.

Indiplon in clinical trials

Indiplon was developed by Neurocrine Biosciences in two distinct formulations. The immediate release form (-IR) was designed to address sleep onset difficulties, while the modified release form (-MR) was developed to help patients stay asleep throughout the entire night. The FDA gave Neurocrine an approvable letter for indiplon-IR 5 and 10 mg in May 2006. Neurocrine plans to resubmit the application in mid-year 2007 after conducting further analyses and modifications to previous analyses. A supplemental pharmacokinetic/food effect profile was also requested by the FDA and has been completed. Indiplon-MR 15 mg was found unapprovable. At the time of this review, Neurocrine may continue to evaluate the MR formulation for sleep maintenance insomnia.

Most of the currently available data on indiplon comes from either abstracts written by researchers involved in studies sponsored by Neurocrine or from corporate press releases. These studies are summarized in Table 1. Additional information from these trials will likely become available as the company begins the market launch of one or both formulations of the drug.

Table 1 Indiplon (-IR and -MR) studies

Authors	Patients (N)	Indiplon dosage	Duration
Rogowski et al 2002	Healthy adults (24)	IR: 15 mg	1 day
Berkowitz et al 2003	Healthy adults (10)	IR: 10 mg	1 day
Roth et al 2003	Healthy adults (228)	IR: 15, 30 mg	1 day
Scharf et al 2004	Healthy adults (593)	IR: 10, 20 mg	1 day
Garber et al 2004	Healthy adults (35)	IR: 10, 20 mg	1 day
Jochelson, Chen et al 2003	Healthy adults (30)	IR: 10, 30, 45 mg	2 weeks
Jochelson et al 2002	Healthy adults and elderly (25)	IR: 15 mg	4 days
Neurocrine Biosciences 2003	Healthy elderly (36)	IR: 5, 10 mg	1 day
Roth et al 2005	Chronic insomniacs (260)	IR: 10, 20 mg	4 weeks
Walsh et al 2004	Chronic insomniacs (194)	IR: 10, 20 mg	5 weeks
Scharf et al 2005	Chronic insomniacs (702)	IR: 10, 20 mg	3 months
Black et al 2006	Chronic insomniacs (536)	IR: 10, 20 mg	12 months
Scharf et al 2003	Elderly chronic insomniacs (42)	IR: 5, 10, 20 mg	1 day
Walsh et al 2005	Elderly chronic insomniacs (358)	IR: 5, 10 mg	2 weeks
Moscovitch et al 2006	Elderly chronic insomniacs (121)	IR: 5, 10 mg	6 months
Corrigan et al 2006	Healthy adults	IR: up to 30 mg	various
Cohn et al 2004	Healthy adults (12)	MR: 30 mg	1 day
Jochelson, Bozigian et al 2003	Healthy adults (36)	MR: 40 mg	1 day
Neurocrine Biosciences 2004d	Healthy adults (325)	MR: 20, 30 mg	1 day
Hull et al 2004	Adults with mild to moderate chronic obstructive pulmonary disease (18)	MR: 20 mg	1 day
Jochelson et al 2004	Chronic insomniacs (211)	MR: 30 mg	2 weeks
Klee et al 2006	Chronic insomniacs (248)	MR: 15 mg	4 weeks
Neurocrine Biosciences 2004b	Chronic insomniacs (740)	MR: 20, 30 mg	3 months
Rosenberg et al 2006	Adult and elderly chronic insomniacs (100)	MR: 15 mg	2 days
Walsh et al 2003	Elderly chronic insomniacs (60)	MR: 10, 20, 30, 35 mg	2 days
Lankford et al 2005	Elderly chronic insomniacs (229)	MR: 15 mg	2 weeks
Neurocrine Biosciences 2004c	Elderly chronic insomniacs (220)	MR: 20 mg	2 weeks
Neurocrine Biosciences 2004a	Elderly chronic insomniacs (340)	MR: 20, 30 mg	5 weeks

Indiplon-IR

Indiplon-IR has been studied in both healthy volunteers and in patients meeting the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV®) criteria for primary insomnia for at least three months (American Psychiatric Association 2000). Two studies induced transient insomnia in healthy adults via a 2-hour phase advance and the sleep laboratory “first night effect.” The impact of indiplon-IR relative to placebo was objectively measured using polysomnography (PSG) in both of these trials (Roth et al 2003; Scharf et al 2004). Objective Latency to Persistent Sleep (LPS) and patient reported Latency to Sleep Onset (LSO) were both significantly improved with all four doses evaluated (10 and 20 mg in the 1st study, 15 and 30 mg in the 2nd). The first study also found that indiplon-IR produced significant improvements in objective and subjective Total Sleep Time (TST, sTST), sleep efficiency and several measures of sleep quality.

Two placebo-controlled trials studied the effects of indiplon-IR (10 and 20 mg) in adults with primary insomnia. The first trial used PSG to measure patient sleep parameters

at the beginning of the first, third and fifth weeks of treatment (Walsh et al 2004). Relative to placebo, both doses of indiplon significantly reduced LPS and patient reports of LSO were also significantly improved at weeks 1 and 5. Significant improvements were also seen in TST (10 mg only) and sleep quality (both doses) at week 1. The second study evaluated subjective sleep parameters over the course of three months (Scharf et al 2005). Patients in this trial reported that indiplon-IR significantly improved the time to sleep onset, sTST, subjective Wake time After Sleep Onset (sWASO) and sleep quality at all time points. A subset of the study population continued treatment for up to 6 months. Improvements in sleep onset were maintained throughout this period of time.

Indiplon-IR was evaluated in two trials with elderly insomnia patients. The first was a dose response study comparing the effects of 5, 10 and 20 mg of indiplon-IR with placebo (Scharf et al 2003). All doses were shown to produce significant improvements in LPS, LSO, sTST and sleep quality. The second study used patient reports to evaluate

the effects of 5 and 10 mg of indiplon relative to placebo (Walsh et al 2005). Both dose levels produced significant improvements in LSO, sTST, the subjective Number of Awakenings (sNAW) and sleep quality during throughout the 2 week treatment period. Additionally, the 10 mg dose group showed significantly improvement in sWASO at both time points. Again, treatment was continued for up to 6 months for a subset of the patients in this trial (Moscovitch et al 2006). Over this extended timeframe, 81% of the study participants randomized to indiplon-IR reported that it improved their sleep (72% on 5 mg, 92% on 10 mg).

Indiplon-MR

Indiplon-MR is an extended release formulation that delivers part of its dose initially and then provides a controlled release of the remainder over the course of the night. It has been tested in studies involving healthy volunteers and in insomnia patients. Transient insomnia was induced in healthy adults via the sleep laboratory model of the “first night effect” and a 2-hour phase advance (Neurocrine Biosciences 2004d). As compared to placebo, PSG measured LPS and subjective LSO were significantly reduced for both doses studied (20 and 30 mg). A second study in healthy adults used repeated venipunctures to simulate sleep maintenance difficulties (Jochelson, Bozigian et al 2003). In this evaluation, indiplon-MR 40 mg significantly improved LSO, sTST and sleep quality relative to placebo. The subjective number of awakenings declined non-significantly, likely due to the stimulus created by multiple instances of blood sampling.

All other indiplon-MR studies were performed with insomnia sufferers, including three trials using adult patients. The first of these three studies randomized patients to either 30 mg of indiplon-MR or placebo (Jochelson et al 2004). Sleep continuity, as measured by sTST, sWASO and sNAW, was significantly improved during the two weeks of treatment with indiplon. Sleep onset and quality also showed significantly improvements at all time points.

The second study lasted for three months and treated the adult patients with either indiplon-MR (20 or 30 mg) or placebo (Neurocrine Biosciences 2004b). Again, measures of sleep maintenance (sTST, subjective Total Wake Time (sTWT), sWASO and sNAW) were significantly improved for both doses over the length of the trial. Participants also reported significant improvements in sleep quality and LSO. The third and final trial in adults compared the indiplon-MR dose submitted for FDA approval (15 mg) with placebo (Klee et al 2006). Patient reports demonstrated significant

improvements in sTST, sWASO, sNAW, sTWT, LSO and sleep quality over the course of the 4 week long study.

Both adult and elderly insomnia patients participated in a placebo-controlled, cross-over PSG study of indiplon-MR 15 mg (Rosenberg et al 2006). Active treatment produced significant improvements in all objective measures of sleep maintenance (WTDS, WASO and TST) and sleep onset. LSO and sleep quality were also significantly improved. Notably, at present this is the only study in the public domain that uses PSG to objectively evaluate indiplon-MR 15 mg in adult patients – the dose submitted to the FDA for approval.

Indiplon-MR has been tested in four trials with elderly insomnia patients. The first of these was a PSG dose-response study comparing indiplon-MR 10, 20, 30 and 35 mg with placebo (Walsh et al 2003). In this trial, significant improvements in WASO and mean sleep efficiency were seen for indiplon-MR doses of 20 mg and above. Relative to placebo, significant improvements in LPS and NAW were demonstrated by all dose levels of active treatment.

Elderly chronic insomnia patients with sleep maintenance difficulties participated in a two week trial of indiplon-MR 20 mg (Neurocrine Biosciences 2004c). At all time points, both sTST and sWASO were significantly improved with treatment. Two investigator global rating scales, subjective sleep maintenance endpoints (sTWT, sNAW), sleep onset and quality were also significantly improved relative to placebo. In another study with elderly patients, indiplon-MR 20 and 30 mg were compared with placebo over a period of 5 weeks (Neurocrine Biosciences 2004a). PSG measured sleep maintenance (WASO, TST, WTDS, and sleep efficiency) and onset (LPS) were significantly improved at all time points. Furthermore, relative to those on placebo, indiplon-MR patients also reported that their sleep quality improved significantly.

Finally, the indiplon-MR dose submitted to the FDA for approval (15 mg) was evaluated in 229 elderly insomnia patients (Lankford et al 2005; Lydiard et al 2006) in a manner similar to that of the adult insomnia patient trial of indiplon-MR 15 mg previously mentioned (Klee et al 2006). As in the adult patient study, the participants in this evaluation reported significant improvement in all sleep measures at all time points. Measures evaluated included sTST, LSO, sWASO, sNAW, sTWT and sleep quality.

Safety and tolerability of indiplon

Indiplon’s safety and tolerability has been assessed in all of the studies reviewed. Overall, few adverse events were

produced by either formulation, and those that did occur were principally consistent with the known effects of hypnotics.

Adverse events were evaluated over the course of a 12 month trial in adult insomnia patients randomized to placebo or indiplon-IR 10 or 20 mg (Black et al 2006). The most frequent adverse events seen at the 20 mg dose level were headaches (8.7%), URI (6.5% and nasopharyngitis (5.9%). The 10 mg group reported headaches (11.8%), back pain and somnolence (both 7.9%). Over the course of the study no clinically relevant changes in vital signs or ECG parameters occurred.

Several pharmacodynamic tests were used across multiple trials to measure the next-day effects of indiplon. The Visual Analog Scales of sleepiness (VAS) was used to measure next day sedation, while the Digit Symbol Substitution Test (DSST) and Symbol Copying Test (SCT) were both used to evaluate residual functional impairment. Across four trials (Roth et al 2003; Scharf et al 2003, 2004; Walsh et al 2004) no changes in any of these next-day measures was observed at any dose level of indiplon-IR studied (5 to 30 mg). Evaluations of indiplon-MR's residual effects have been reported for two trials. Only the highest dose evaluated (35 mg) was shown to produce a modest effect on DSST scores (Walsh et al 2003; Lydiard et al 2006). No other impairment or evidence of residual sedation was found.

The potential for the development of tolerance and withdrawal symptoms resulting from indiplon was examined across several studies. A 2-week repeat dosing study in healthy volunteers found no evidence of PK or PD tolerance with indiplon-IR (Jochelson, Chen et al 2003). Three additional trials in insomnia sufferers incorporated the Benzodiazepine Withdrawal Symptom Questionnaire (Walsh et al 2004, 2005; Scharf et al 2005). Using this scale, no signs of withdrawal were found during treatment that lasted up to 3 months with indiplon-IR 5 to 20 mg.

In spite of warnings against doing so, insomnia patients often consume hypnotics and alcohol together. Co-administration of these compounds often leads to changes in drug PK which may, in turn, result in additive impairment. The interaction of indiplon-IR and alcohol was evaluated to assess the likelihood of these effects (Berkowitz et al 2003). This study found a small, non-additive reduction in performance on pharmacodynamic tests (DSST and SCT). Reaction time and sedation (VAS) were unaffected.

Studies of healthy volunteers have assessed the potential for drug-drug interactions between indiplon and several other compounds (Corrigan et al 2006). These evaluations have

found that indiplon does not impact the PK of either digoxin or theophylline. The PK and PD of warfarin also remained unaffected. Co-administration of indiplon with antidepressants (sertraline, paroxetine, venlafaxine, amitriptyline) does not result in additive effects on PD assessments and appears to have no effect on indiplon's PK values.

Respiratory depression in individuals with chronic obstructive pulmonary disease (COPD) and sleep apnea has been observed when individuals from these at-risk group use benzodiazepine hypnotics. Unfortunately, sleep apnea and COPD are strongly linked with co-morbid insomnia, creating complex treatment trade-offs (Fleetham et al 1982; Weiss et al 2000). Indiplon-MR's respiratory depressant effects were assessed in COPD patients to evaluate the risk indiplon presents for this patient subset (Hull et al 2004). Relative to placebo, no changes in either the arterial oxygen saturation level or the respiratory disturbance index were produced by single night of indiplon-MR 20 mg. Additionally, half of the individuals receiving indiplon reported "very good" or "excellent" sleep quality vs only 17% of those randomized to placebo. Indiplon-MR 30 mg was compared to codeine sulfate 60 mg (active control) and placebo in a daytime CO₂ challenge model (Cohn et al 2004). After dosing with codeine, healthy volunteers experienced respiratory suppression for 8 hours. In contrast, no respiratory effects were demonstrated at any time point following administration of indiplon.

Finally, middle of the night dosing with indiplon-IR was evaluated. Existing therapeutics are not appropriate for insomniacs who awaken in the middle of the night and have difficulties returning to sleep because these medications' relatively long duration of action can produce significant next day impairments when taken with less than 8 hours available time in bed. The next-day effects of taking indiplon-IR with only 4 hours remaining time in bed were studied in three separate trials. Two of these trials also incorporated other hypnotics as comparators.

A single-night, cross-over study in healthy adults woke participants after they had spent only 4 hours in bed (Garber et al 2004). Volunteers were dosed with either indiplon-IR (10 or 20 mg), zolpidem 10 mg, zopiclone 7.5 mg or placebo and were then permitted to remain in bed for another 4 hours before being awakened a second time. Participants performed the DSST, SCT and VAS at 4 and 6 hours post-dose to assess the relative next-day residual effects of study treatment. Relative to placebo, indiplon-IR was the only drug that did not produce any significant changes on any of these tests. Zolpidem produced a significant increase in

sleepiness at 4 hours post-dose and significantly increased sedation was seen at both 4 and 6 hours post-dose with zopiclone.

Healthy elderly volunteers participated in a similar trial comparing the effects of 5 and 10 mg of indiplon-IR, following middle of the night dosing, with those resulting from 3.75 mg of zopiclone and placebo (Neurocrine Biosciences 2003). As in the study with young adults, neither dose of indiplon-IR produced any significant changes on the DSST, SCT or VAS at any time point. Participants randomized to zopiclone, however, demonstrated significant changes on the DSST at 4 and 8 hours post-dose and showed a trend toward impairment on the SCT at both 4 and 6 hours post-dose.

The third study of middle of the night dosing was conducted in adult insomnia patients on an outpatient basis (Roth et al 2005). Over the course of 4 weeks, double-blind therapy (indiplon-IR 10 or 20 mg, placebo) was self administered on a *prn* basis as long as at least 4 hours sleep time was available to the patient. Participants reported that LSO post-dose was significantly shortened at all time points. Furthermore, over the course of the study, the average sTST was significantly extended for patients randomized to both doses of indiplon-IR relative to those treated with placebo. VAS ratings showed no increase in next day sleepiness at either dose of active treatment.

Summary

Indiplon is a novel sedative-hypnotic that modulates subunits of the GABA receptor complex in order to induce sedation. It has been shown to be well tolerated and effective as an insomnia therapy in randomized, placebo-controlled trials involving more than 7,500 participants. Both patient reported and objectively measured sleep parameters have shown consistent improvements without next-day residual sedation or impairment. Indiplon was developed in two different formulations to address two different types of insomnia complaint: indiplon-IR (immediate release) was designed for sleep onset difficulties, while indiplon-MR (modified release) was developed for sleep maintenance insomnia. Indiplon-IR shows potential for use on a *prn* basis, for example, by patients who wake in the middle of the night and are unable to return to sleep without assistance.

Disclosures

Dr Lankford has been an investigator in clinical trials covered in this review. He has also served on an advisory board for Neurocrine Biosciences.

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