Indiplon: A Nonbenzodiazepine Sedative–Hypnotic for the Treatment of Insomnia

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OBJECTIVE: To review the pharmacology, pharmacokinetics, pharmacodynamics, efficacy data, and adverse effects of indiplon in the treatment of transient and chronic insomnia in adult and geriatric patients.

DATA SOURCES: A literature search was conducted using MEDLINE (1966–May 2008), *International Pharmaceutical Abstracts* (1970–May 2008), and Cochrane database (2007) for the key words indiplon or NBI-34060. References cited in the articles were reviewed for additional information. Abstract data were included only in the absence of significant published data.

STUDY SELECTION AND DATA EXTRACTION: English-language literature reporting animal and human clinical studies was reviewed to evaluate data on the pharmacology, pharmacokinetics, pharmacodynamics, efficacy, and adverse effects of indiplon. Clinical trials selected for inclusion were limited to those with human subjects, with the accepted inclusion of pharmacology data in animals.

DATA SYNTHESIS: Indiplon is a nonbenzodiazepine sedative–hypnotic that exhibits its sedating activity through its interaction with the γ-aminobutyric acid α receptor complex. Indiplon immediate-release (IR) as well as modified-release (MR) forms have shown improvement compared with placebo in patients with DSM-IV-TR primary insomnia in various areas of subjective and objective sleep measurements. Specifically, improvements in total sleep time, latency to persistent sleep, latency to sleep onset, wake after sleep onset, and sleep quality have been noted in clinical trials. Trials evaluating both indiplon IR and MR have so far not identified any major serious adverse effects.

CONCLUSIONS: Limited clinical trial data exist on use of indiplon in a "true" transient insomnia patient population. Based on recent Food and Drug Administration requests, clinical trial data assessing direct comparisons of indiplon IR with other approved nonbenzodiazepine sedative–hypnotics are needed to clearly define the differences among these agents.

KEY WORDS: indiplon, insomnia, nonbenzodiazepine sedative–hypnotic.

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The *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (DSM-IV-TR) describes primary insomnia as a disorder with multiple essential symptoms. These symptoms include difficulty falling asleep, intermittent wakefulness during sleep, waking up too early, or nonrestorative sleep.[1] Insomnia is a very common problem in the general adult population. It has been reported that 10% of the adult population suffers from chronic insomnia and more than half of the adult population in the US reports having symptoms of insomnia at least a few nights a week.[2-5] Individuals who have multiple medical conditions, take a large number of medications regularly, and/or have changes in sleep architecture describe having the most problems with sleep disturbances. As the number of medical conditions increases, the more likely an individual is to report having fair-to-poor quality of sleep compared with good-to-excellent sleep.[5]

Insomnia treatment is focused on improving the quantity and quality of sleep. Katz and McHorney[6] reported that 85% of patients with severe insomnia and at least one chronic medical condition still

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had moderate-to-severe sleep complaints in a 2-year follow-up that analyzed 5 sleep domains including: initiation and maintenance of sleep, respiratory problems during sleep, quantity of sleep, perceived adequacy of sleep, and daytime somnolence. Improvements may be seen in a variety of sleep parameters, but these are often not sustainable over time with medication treatment. Benzodiazepines have been used in the treatment of insomnia dating back to the 1960s.[7] In the 1980s, studies began to evaluate nonbenzodiazepine sedative–hypnotics (NSHs) for the management of insomnia. The rationale for studying NSHs was related to the fact that benzodiazepines bind to multiple benzodiazepine receptors in a nonselective fashion (contributing to unwanted effects) compared with NSHs and, more specifically, the benzodiazepine receptor agonists bind to the α-1 and/or α-3 subunits of the γ-aminobutyric acid (GABA) receptor, but not to the α-2 subunits.[7] Benzodiazepine receptor agonists' selective binding helps to minimize the unwanted anxiolytic and muscle relaxant effects seen with benzodiazepines. Today there are 2 main classes of NSHs: the benzodiazepine receptor agonists and the melatonin receptor agonists. Since 1993, the Food and Drug Administration (FDA) has approved 5 NSHs (4 benzodiazepine receptor agonists, 1 melatonin receptor agonist) for the treatment of insomnia. The sleep agent zolpidem tartrate accounts for 2 of the FDA-approved drugs including an immediate-release (IR) and controlled-release formulation. An oral disintegrating tablet form of zolpidem tartrate was tentatively approved by the FDA on April 21, 2005, but Bioavail, the manufacturer, has yet to seek full FDA approval of the product.[8] Table 1 depicts the key pharmacokinetic properties, doses, and indications of NSHs approved for use in the management of insomnia.[9-18]

Indiplon, an NSH (specifically, a benzodiazepine receptor agonist), has been studied in clinical trials over the past 5 years. The focus of evaluating indiplon in patients with sleep disturbances had been related to the drug's highly selective binding capacity at the α-subunit of the GABA receptor. Neurocrine Biosciences, Inc., owns the proprietary rights to indiplon and has studied both an IR and modified-release (MR) formulations. On June 12, 2007, a New Drug Application for indiplon IR 5- and 10-mg capsules for the treatment of insomnia was submitted to the FDA.[19] On December 12, 2007, the FDA sent the company a letter stating that these formulations are approvable for the treatment of insomnia, pending additional trial data. Specifically, clinical information evaluating the elderly population and general safety data comparing indiplon with other insomnia agents have been requested. Safety of indiplon in the third trimester of pregnancy warrants evaluation as well.[19] An evaluation of indiplon and its role in the management of insomnia needs to be performed specifically focusing on efficacy and safety.

Data Sources and Selection

A literature search was conducted using MEDLINE (1966–November 2007), *International Pharmaceutical Abstracts* (1970–November 2007), and Cochrane database (2007) for the key words indiplon or NBI-34060. References cited in the articles were reviewed for additional information. Abstract data were included only in the absence of significant published data. English-language literature reporting animal and human clinical studies was reviewed to evaluate the pharmacology, pharmacokinetics, pharmacodynamics, efficacy data, and adverse effects of indiplon. Clinical trials selected for inclusion were limited to those with human subjects, with the accepted inclusion of pharmacology data in animals.

Pharmacology

Indiplon is a pyrazolopyrimidine. It possesses pharmacologic properties similar to those of the benzodiazepines including anxiolytic, hypnotic, and sedative activity. The GABA α-1 subunits are known to mediate sedation, the α-2 and α-3 subunits have been suggested to mediate anxiolytic and myorelaxation effects, and the α-5 subunits are associated with cognition and processing based on many rodent studies.[20] Most NSHs have been designed with selectivity for the GABA α-1 subunit to increase the sedative properties while minimizing the other unwanted effects

Table 1. FDA-Approved Dosing of Nonbenzodiazepine Sedative–Hypnotics[9-18]

Drugs	Duration of Action	Half-Life (h)	Adult Dose (mg)	Elderly Dose (mg)	Insomnia Indication
Benzodiazepine receptor agonists					sleep onset and maintenance
eszopiclone	intermediate	6	2–3	1	
zaleplon	ultrashort	1	10	5	
zolpidem	short	2.6	10	5	
zolpidem CR	intermediate	2.8	12.5	6.25	
Melatonin receptor agonist					sleep onset
ramelteon	short	2–5	8	8	

CR = controlled release; FDA = Food and Drug Administration.

that are noted with the α-2, α-3, and α-5 subunits. Sullivan et al.[21] originally looked into the GABA binding of indiplon in rats and proposed that it may be more selective for the α-1 subunit. Petroski et al.[22] further studied the interaction and determined the selectivity of indiplon for individual subunits of the recombinant rodent GABA α receptors. Indiplon's selectivity for the α-1 subunit proved to be 10 times that of the α-2, α-3, or α-5 subunits. The half maximal effective concentrations were 2.6, 24, 60, and 77 nM for α-1, α-2, α-3, and α-5 subunits, respectively. Zolpidem's and zopiclone's selectivity for the α-1 subunit proved to be 5 times that of the α-2, α-3, or α-5, while zaleplon was only twice as selective. Indiplon's selectivity for the α-1 subunit has been demonstrated to be greater than that of other NSHs, but its mechanism of sedation is still mediated through the same subunit modulation of the GABA receptor.

Biopharmaceutics, Pharmacokinetics, Pharmacodynamics

In pharmacokinetic studies involving humans, the peak plasma concentration of indiplon has been reported at 0.73 and 0.82 hours and the half-life elimination time of 1.97 and 1.71 hours in healthy males and females, respectively.[23] One study reported no age-related difference in pharmacokinetic profiles of indiplon in human subjects.[24] The mean time to plasma concentrations of indiplon peaked at 2.3 and 1.5 hours, with a half-life elimination time of 1.5 and 1.8 hours in young adults and elderly individuals, respectively. In both human pharmacokinetic studies, there were no statistically significant differences between sex or age in relation to the time to peak plasma concentrations and elimination half-lives.

Indiplon is metabolized through 2 separate metabolic pathways. *N*-Demethylation of indiplon is catalyzed by CYP3A4/5 and forms the inactive metabolite *N*-desmethyl indiplon. This pathway accounts for 60–70% of the drug's clearance through human liver microsomes.[25] *N*-Deacetylation of indiplon is catalyzed by carboxyl-esterases and results in formation of the inactive metabolite *N*-desacetyl indiplon. *N*-Desmethyl-desacetyl indiplon is the third and minor inactive metabolite, which is formed through the *N*-deacetylation of *N*-desmethyl indiplon and the *N*-demethylation of *N*-desacetyl indiplon. Indiplon undergoes extensive metabolism, resulting in less than 1% being excreted as unchanged indiplon in urine and feces.

Pharmacodynamic effects and their relation to pharmacokinetic principles are important to evaluate in all medications. Chronic use of benzodiazepines often produces both pharmacokinetic and pharmacodynamic changes resulting in the formation of tolerance. Pharmacokinetic tolerance refers to any change in distribution or metabolism of a drug following repeated exposure that results in a lower blood concentration with the administration of the same initial dose.[26] Pharmacodynamic tolerance refers to adapted changes that result in reduced drug activity following administration of the same dose. The development of tolerance was studied in a group of 30 healthy adults taking indiplon 10, 30, or 45 mg daily over 2 weeks.[27] Indiplon absorption and elimination rates were unchanged between day 1 and day 14, suggesting no pharmacokinetic tolerance after repeated doses. Electroencephalograms were monitored on a daily basis and showed decreases in occipital and cortical α waves, but these are known changes of sedative–hypnotics, and these changes were similar on day 1 and day 14, indicating no pharmacodynamic tolerance following 2 weeks of daily indiplon therapy.

Clinical Studies

The safety and efficacy of indiplon IR treatment in simulated transient insomnia in healthy volunteers and patients with chronic insomnia have been investigated in 10 randomized, double-blind, placebo-controlled trials and 1 open-label extension trial in 3105 subjects between 18 and 80 years of age.[11,12,28-41] Indiplon MR was investigated in 4 additional randomized, double-blind, placebo-controlled trials in 536 individuals between 19 and 85 years of age.[9,10,30-34] The manufacturer of indiplon sponsored all clinical trials. Some data are limited to abstract form. Table 2[28-36,41] and Table 3[37-40] provide a summary of the indiplon IR and indiplon MR studies, respectively.

IMMEDIATE-RELEASE FORMULATION STUDIES

Adults

The efficacy of indiplon IR was studied in a healthy adult population during 2 clinical trials. Roth et al.[28] evaluated healthy adults by inducing transient insomnia through the introduction of an unusually early bedtime. Subjects received indiplon IR 15 mg, indiplon IR 30 mg, or placebo. Latency to persistent sleep (LPS) was reduced in both indiplon groups, with mean values of 17.5 and 16.2 minutes for the 15- and 30-mg doses, versus 43.1 minutes for placebo ($p < 0.001$). Latency to sleep onset (LSO) was also significantly improved, with mean values of 15.8 and 15.4 minutes for the 15- and 30-mg doses, versus 31.1 minutes for placebo ($p < 0.001$). No improvements in total sleep time (TST) were noted. In a similar study, patients were randomized to receive indiplon IR 10 mg, indiplon IR 20 mg, or placebo.[29] LPS was reduced in both indiplon groups, with mean ± SEM values of 21.2 ± 1.5 and 16.8 ± 1.1 minutes for the 10- and 20-mg doses versus 33.1 ± 2.5 minutes for placebo ($p < 0.0001$). TST mean values were also improved with both the 10- (414.5 ± 3.9 min) and 20-mg doses (432.5 ± 3.1 min) compared with placebo (402.9 ± 3.9 min; $p < 0.005$ for 10 mg; $p < 0.0001$ for 20 mg). Im-

provements in sleep quality with both doses were reported. Significant improvement in mean wake after sleep onset (WASO) time with 20 mg compared with placebo also occurred, with values of 42.5 ± 2.8 and 49.9 ± 2.9 minutes, respectively ($p = 0.0091$). The number of awakenings reported after sleep onset (NAASO) was reduced by 1 per night with 20 mg versus placebo ($p < 0.0001$). Limitations to the applicability of these 2 studies exist secondary to the fact that each was only one night and the population was only healthy adults versus a true transient insomnia population.

Three studies evaluated use of indiplon IR in adults meeting the DSM-IV-TR criteria of chronic insomnia for

Table 2. Indiplon Immediate-Release Studies[28-36,41]

Reference	Design	Subjects	Dose	Duration	Efficacy	ADEs
Black (2006)[41]	R, DB, PG	N = 533 age 21–64 y DSM-IV-TR primary insomnia	indiplon 10, 20 mg	12 mo	NA	serious AE <1%
Farber (2008)[33]	R, DB, PC, 5-way cross-over	N = 35 age 18–45 y (mean 32) healthy adults	indiplon 10, 20 mg zolpidem 10 mg zopiclone 7.5 mg placebo	1 day	no statistically significant changes noted in VAS-S at 4 and 6 h	placebo = 8.6% indiplon 10 mg = 5.9% indiplon 20 mg = 11.8% zolpidem = 11.4% zopiclone = 29%
	R, DB, PC, 4-way cross-over	N = 35 age 65–71 y (mean 68) healthy elderly	indiplon 5, 10 mg zolpiclone 3.75 mg placebo	1 day	no statistically significant changes noted in VAS-S at 4, 6, and 8 h	indiplon 5 mg = 2.8% indiplon 10 mg = 2.8% zopiclone = 0% placebo = 2.8%
Moscovitch (2006)[36]	OL, extension	N = 121 age 65–80 y (mean 71) DSM-IV-TR primary insomnia	indiplon 5, 10 mg	6 mo	81% reported improved sleep, mean doses 22/mo	indiplon 5 mg = 57% indiplon 10 mg = 65% serious AE = 7%
Rosenburg (2007)[29]	R, DB, PC, MC, PG	N = 593 age 21–64 y (mean 32) healthy adults	indiplon 10, 20 mg placebo	1 day	↓ LPS, ↑ TST, ↓ WASO (20 mg only), ↓ NAASO (20 mg only), ↑ sleep quality	no serious AE
Roth (2003)[28]	R, PC, MC, PG	N = 228 age 18–59 y (mean not reported) healthy adults	indiplon 15, 30 mg placebo	1 day	↓ LPS, ↓ LSO	no serious AE
Roth (2007)[30]	R, DB, PC, PG	N = 264 age 18–64 y (mean 46) DSM-IV-TR primary insomnia	indiplon 10, 20 mg placebo	28 days	↓ LSO, ↑ self-reported TST, ↑ sleep quality, ↓ self-reported WASO (20 mg only), ↓ self-reported NAASO (20 mg only)	placebo = 26% indiplon 10 mg = 39% indiplon 20 mg = 34%
Scharf (2003)[34]	R, DB, PC, MC, 4-period crossover	N = 42 age 65–82 y (mean 70) DSM-IV-TR primary insomnia	indiplon 5, 10, 20 mg placebo	1 day	↑ TST, ↓ LPS, ↓ LSO	no serious AE
Scharf (2007)[31]	R, DB, PC, MC	N = 702 age 21–64 y (mean 46) DSM-IV-TR primary insomnia	indiplon 10, 20 mg placebo	3 mo	↓ self-reported LSO, ↑ self-reported TST, ↓ self-reported WASO, ↓ self-reported NAASO, ↑ sleep quality	no serious AE
Walsh (2007)[35]	R, DB, PC	N = 358 age 65–80 y (mean 71) DSM-IV-TR primary insomnia	indiplon 5, 10 mg placebo	14 days	↓ LSO, ↑ self-reported TST, ↓ self-reported NAASO, ↓ self-reported WASO (10 mg only)	placebo = 0.8% indiplon 5 mg = 5.0% indiplon 10 mg = 8.4%
Walsh (2004)[32]	R, DB, PC	N = 194 age 29–52 y (mean 40.2) DSM-IV-TR primary insomnia	indiplon 10, 20 mg placebo	35 days	↓ LPS, ↓ LSO, ↑ TST (wk 1 only), ↑ sleep quality (wk 1 only)	no serious AE

ADEs = adverse drug events; AE = adverse effect; DB = double-blind; LPS = latency to persistent sleep; LSO = latency to sleep onset; MC = multicenter; NA = not available; NAASO = number of awakenings after sleep onset; OL = open-label; PC = placebo-controlled; PG = parallel group; R = randomized; TST = total sleep time; VAS-S = Visual Analog Scale of Sleepiness; WASO = wake after sleep onset.

at least 3 months prior to study enrollment. Roth et al.[30] evaluated patients with primary chronic insomnia over 4 weeks using indiplon IR 10 mg, indiplon IR 20 mg, or placebo. LSO after indiplon dosing following a middle of the night (MOTN) awakening was significantly improved with mean values of 36.5 ($p = 0.0023$) and 34.4 minutes ($p < 0.0001$) with 10 and 20 mg, versus 45.2 minutes with placebo. Subjective TST was significantly improved with both 10 and 20 mg, with mean values of 253 and 278 minutes, respectively, compared with 229 minutes in the placebo group ($p < 0.01$). Sleep quality was also improved with both doses ($p < 0.0001$). The 20-mg dose resulted in significant reductions in WASO ($p = 0.0122$) and NAASO ($p = 0.0125$) compared with placebo. In a 3-month study, patients with documented primary chronic insomnia received indiplon IR 10 mg, indiplon IR 20 mg, or placebo.[31] The primary endpoint of subjective LSO was significantly improved at one month, with mean values of 15.8 ± 1.3 and 33.0 ± 1.3 minutes for the 10- and 20-mg doses, respectively, versus 48.7 ± 1.9 minutes for placebo ($p < 0.0001$). Subjective TST was significantly improved with both 10 and 20 mg, with mean values of 364.8 ± 4.6 and 372.8 ± 4.8 minutes at 3 months, respectively, compared with 338.2 ± 4.9 minutes with placebo ($p < 0.0001$). Secondary endpoints of WASO, NAASO, and sleep quality were all significantly improved at 3 months with both doses. The third study randomized patients with primary chronic insomnia to receive indiplon IR 10 mg, indiplon IR 20 mg, or placebo over 5 weeks.[32] LPS at week 5 of the study was significantly improved, with mean values of 29.2 ($p < 0.01$) and 24.8 ($p < 0.05$) minutes for the 10- and 20-mg doses, respectively, compared with 40.1 minutes for placebo. Subjective LSO was improved with both doses at week 5 compared with placebo ($p < 0.02$). TST and sleep quality were significantly improved at week 1, but early improvements diminished by week 5.

Farber and Burke[33] performed the only study that evaluated indiplon and other NSH agents in the same study in both the adult and elderly population. The adult study was a single-center, randomized, double-blind, 5-way crossover trial that included 35 patients receiving indiplon IR 10 mg, indiplon IR 20 mg, zolpidem 10 mg, zopiclone 7.5 mg, and placebo. The study was designed to assess the residual effects of MOTN dosing of sedative–hypnotics. No significant changes in the visual analog scale (VAS) of sleepiness were noted with either dose of indiplon versus placebo at 4 and 6 hours postdose. Zolpidem showed significant increases in the VAS sleepiness score at 4 hours ($p = 0.042$), but not at 6 hours. Zopiclone showed statistically significant increases in the VAS sleepiness score at both 4 hours ($p < 0.0001$) and 6 hours ($p = 0.0002$). The lack of next-day residual following MOTN dosing of indiplon is logical based on the drug's short elimination half-life.

Elderly

The efficacy of indiplon IR has been studied in an elderly population. Scharf et al.[34] randomized elderly patients with primary chronic insomnia to receive indiplon IR 5 mg, indiplon IR 10 mg, indiplon IR 20 mg, or placebo for one night in a crossover fashion. Indiplon demonstrated a significant improvement in LPS, with mean values of 13.8, 10.4, and 9.8 minutes for 5, 10, and 20 mg, respectively, versus 25.2 minutes for placebo ($p < 0.001$). Indiplon IR 10 and 20 mg showed significant improvements in TST

Table 3. Indiplon Modified-Release Studies[37-40]

Reference	Design	Subjects	Dose	Duration	Efficacy	ADEs
Jochelson (2003)[37]	R, DB, PC, PG	N = 36 age 19–42 y healthy adults	indiplon 40 mg placebo	1 day	↓ LSO, ↑ TST, ↑ sleep quality	no serious AE
Jochelson (2004)[38]	R, DB, PC	N = 211 mean age 48 y DSM-IV-TR primary insomnia	indiplon 30 mg placebo	14 days	↑ self-reported TST, ↓ self-reported WASO, ↓ LSO, ↓ self-reported NAASO, ↑ sleep quality	no serious AE
Lydiard (2006)[40]	R, DB, PC, PG	N = 229 age 65–85 y (mean 71) DSM-IV-TR primary insomnia	indiplon 15 mg placebo	14 days	↓ LSO, ↑ TST, ↓ self-reported WASO, ↓ self-reported NAASO, ↑ sleep quality	2 serious AEs not related to study drug
Walsh (2003)[39]	R, DB, PC, latin-square design	N = 60 age 65–72 y (mean 69) DSM-IV-TR primary insomnia	indiplon 10, 20, 30, 35 mg placebo	2 days	↓ LPS, ↓ WASO (20, 30, 35 mg), ↑ SE (20, 30, 35 mg)	no serious AE

ADEs = adverse drug events; AE = adverse effect; DB = double-blind; LPS = latency to persistent sleep; LSO = latency to sleep onset; NAASO = number of awakenings after sleep onset; PC = placebo-controlled; PG = parallel group; R = randomized; SE = sleep efficiency; TST = total sleep time; WASO = wake after sleep onset.

with mean values of 372.1 ($p = 0.027$) and 385.6 minutes ($p < 0.001$). LSO for indiplon IR 5, 10, and 20 mg resulted in values of 28.8, 24.7, and 20.2 minutes, respectively, versus 41.8 minutes for placebo ($p < 0.004$). In another study, elderly patients with primary chronic insomnia received indiplon IR 5 mg, indiplon IR 10 mg, or placebo over 2 weeks.[35] Significant improvements in mean LSO time ± SD were seen with both 5 mg (34.6 ± 1.8 min) and 10 mg (30.4 ± 1.6 min) relative to placebo (47.4 ± 2.5 min) at week 1 ($p < 0.0001$). Subjective TST was significantly improved with both the 5- and 10-mg doses, with mean values of 340.3 ± 5.0 and 360.0 ± 5.0 minutes at week 1, respectively, compared with 312.2 ± 5.0 minutes with placebo ($p < 0.0001$). Subjective NAASO and sleep quality were significantly improved in both doses at 2 weeks, but 10 mg was the only dose that significantly improved WASO at 2 weeks. An open-label extension trial evaluated adults over a 6-month period, with indiplon IR 5 and 10 mg used as needed.[36] Subjective sleep improvement rates were 72% and 92% for the 5- and 10-mg doses, respectively. Two-thirds of patients remained in the study for all 6 months, with only 5 patients in the 5-mg group withdrawing from the study for lack of efficacy.

Similar to the adult study, Farber and Burke[33] performed a single-center, randomized, double-blind, 4-way crossover trial including 35 elderly patients who received indiplon IR 5 mg, indiplon IR 10 mg, zopiclone 3.75 mg, and placebo. The study was designed to assess the residual effects of MOTN dosing of sedative–hypnotics. No significant changes in the VAS sleepiness score were noted with either the 5- or 10-mg dose of indiplon versus placebo at 4, 6, and 8 hours postdose.

MODIFIED-RELEASE FORMULATION

Adults

The efficacy of indiplon MR has been studied in a healthy adult population. Jochelson et al.[37] randomized healthy adults to receive indiplon MR 40 mg or placebo for one night during a pharmacokinetics study designed to simulate a transient insomnia patient population. LSO was reported as 30.2 minutes and 72.2 minutes with 40 mg and placebo, respectively ($p < 0.001$). TST was also significantly improved, with mean values of 315.6 and 246.6 minutes for 40 mg and placebo, respectively ($p < 0.02$). Significant improvements in sleep quality were reported with the 40-mg dose ($p = 0.04$). Another study by Jochelson et al.[38] evaluated 211 adults with primary chronic insomnia over 2 weeks. Patients were randomized to receive indiplon MR 30 mg or placebo. The primary endpoint of subjective TST was significantly increased with the 30-mg dose relative to placebo both at week 1 (375 vs 328 min; $p < 0.0001$) and at week 2 (367 vs 336 min; $p = 0.0013$). Subjective WASO times were 54 and 79 minutes for 30 mg and placebo, respectively, at week 1 ($p < 0.0001$) and 51 and 73 minutes at week 2 ($p = 0.0003$). Improvements in LSO ($p = 0.0131$) and sleep quality ($p < 0.0001$) were seen in the 30-mg group at week 2. The extent of clinical trials evaluating indiplon MR is limited compared with the number of patients who have received indiplon IR in clinical trials.

Elderly

The efficacy of indiplon MR has also been studied in the elderly population. Elderly patients with primary chronic insomnia were randomized to receive indiplon MR 10, 20, 30, or 35 mg, or placebo over a 2-day period.[39] LPS was significantly improved in all indiplon groups. Specifically, the mean LPS values were 17.2, 11.2, 11.0, 9.9, and 26.0 minutes with 10, 20, 30, and 35 mg, and placebo, respectively ($p < 0.01$). WASO was significantly improved with 20, 30, and 35 mg doses noted by values of 87.3, 81.9, and 83.0 minutes, respectively, versus 103.2 minutes for placebo ($p < 0.01$). Sleep efficiency was significantly improved with the 3 highest doses of indiplon versus placebo ($p < 0.0001$). In a trial lasting 2 weeks, elderly patients with primary chronic insomnia were randomized to receive indiplon MR 15 mg or placebo.[40] TST was significantly improved with 15 mg compared with placebo at week 1, with mean ± SD values of 377 ± 4 and 328 ± 4 minutes, respectively ($p < 0.0001$). Significant improvements were seen in LSO ($p < 0.001$), subjective WASO ($p < 0.001$), subjective NAASO ($p < 0.001$), and sleep quality ($p < 0.001$) for indiplon versus placebo at both weeks 1 and 2.

The elderly population made up more than 50% of the patients evaluated using indiplon MR, but overall it accounted for only 22% of the patients who received either indiplon IR or MR in clinical trials.

Adverse Effects

The safety of indiplon IR and MR has been evaluated over the past 5 years in Phase 1 through 3 studies. Currently, no serious adverse effects have been attributed to indiplon treatment based on clinical trial data. In the largest trial, the most common adverse effects were upper respiratory infection (placebo 5.2%, indiplon IR 10 mg 5.9%, indiplon IR 20 mg 6.0%), amnesia (placebo 3.0%, indiplon IR 10 mg 1.3%, indiplon IR 20 mg 6.4%), dizziness (placebo 3.0%, indiplon IR 10 mg 4.7%, indiplon 20 mg 6.9%), headache (placebo 6.9%, indiplon IR 10 mg 8.5%, indiplon IR 20 mg 9.0%), and somnolence (placebo 1.3%, indiplon IR 10 mg 3.0%, indiplon IR 20 mg 7.3%).[31] The adverse effects that have occurred are largely consistent with the known effects of sedative–hypnotics. To date, only 2 patients in published clinical trials have suffered serious adverse effects while taking indiplon. One patient de-

veloped a small bowel obstruction and the other experienced vertigo, neither of which was determined to be related to indiplon as judged by the study investigators.[31]

The safety of indiplon IR 10 and 20 mg has been evaluated in one randomized, parallel-group, 12-month safety study. Black et al.[41] randomized 533 adults with primary chronic insomnia to receive indiplon IR 10 or 20 mg. Overall, 43.8% and 37.5% of patients, respectively, completed all 12 months of the study. The adverse effects occurring in 5% or more of patients in the 10-mg group included back pain (7.9%), sinusitis (5.1%), arthralgias (5.1%), nasopharyngitis (5.6%), upper respiratory infection (5.6%), nausea (6.7%), somnolence (7.9%), and headaches (11.8%). Some of the NSHs (eg, zolpidem) have been linked to nocturnal activities (eg, sleep driving, binge eating), but to this point, there have been no reports of these activities with indiplon.

A lack of tolerance effect was reported in the one study evaluating indiplon following 2 weeks of nightly dosing.[27] A 3-month study of nightly indiplon reported that rebound insomnia occurred in 8.8%, 18.9%, and 22.1% of patients on the first night of discontinuation for placebo, indiplon IR 10 mg, and indiplon IR 20 mg, respectively.[31] Rebound insomnia was present on night 2 following discontinuation for 1.1%, 11.1%, and 11.4% for placebo, indiplon IR 10 mg, and indiplon IR 20 mg, respectively.

Carter et al.[42] evaluated the abuse potential of indiplon compared with triazolam. The investigators determined that the abuse potential did not differ between the drugs, but the psychomotor and cognitive impairment at large doses (30, 50, and 80 mg) of indiplon might be less than with triazolam. This determination was based on the fact that the slope of the dose–effect curve of measured sedation for triazolam was greater than that of indiplon. The determination that abuse potential exists with indiplon is related to the fact that indiplon interacts through the GABA α-1 subunit and to a lesser degree the α-2, α-3, and α-5 subunits. Abuse potential is linked to the anxiolytic effects of the α-2 and α-3 subunits. Further study in this area is warranted to establish long-term safety and tolerability.

Contraindications

To date, published reports of indiplon use are limited to describing its use in healthy adult and elderly volunteers and patients with DSM-IV-TR primary chronic insomnia. Indiplon is contraindicated in patients with hypersensitivity or allergic reactions to previous exposures. Patients with a history of substance abuse or chronic alcohol consumption (≥5 alcoholic beverages/day or ≥14 alcoholic beverages/wk) were excluded from the indiplon clinical trials. Precaution in patients with hepatic impairment may be warranted since indiplon is almost 100% metabolized in the liver. The drug's safety during pregnancy has yet to be evaluated and is the reason for the FDA's recent request for Neurocrine Biosciences, Inc., to provide safety data on the administration of indiplon during the third trimester of pregnancy.[12] Further investigation may identify other relevant precautions.

Drug Interactions

Indiplon is a weak inhibitor of CYP1A2, 2C8, and 2C9, with a 0.3% calculated fractional inhibition for all 3 enzymes. These findings make the potential for drug–drug interactions resulting from cytochrome P450 inhibition quite low.[21,25] A small potential risk does remain secondary to the fact that indiplon is a substrate for CYP3A4/5 and 1A2, with CYP 3A4/5 being the main enzymes responsible for the *N*-demethylation of indiplon in the liver. Coadministration of CYP3A4/5 inhibitors (ketoconazole and erythromycin) did result in increases of plasma area under the curve (AUC) for indiplon of 1.25–2.4 times the normal range.[25] The administration of a rifampin, a CYP3A4/5 inducer, resulted in a decrease in plasma AUC of indiplon by 70%.[25] Coadministration of a strong CYP3A4/5 inhibitor could result in a moderate increase in indiplon exposure and subsequently a strong CYP3A4/5 inducer could result in a decrease in exposure to indiplon. Precaution with coadministration of these products is therefore warranted. Coadministration of alcohol (0.7 mg/mL) with indiplon IR 10 mg has been studied in healthy volunteers and resulted in no pharmacokinetic interactions.[43] The pharmacodynamic changes noted in the combination group (indiplon and alcohol) were related to reductions in performance as measured by the digital symbol substitution test and the symbol copying test, while sedation and reaction time measures remained the same. Despite no pharmacokinetic interactions with alcohol, there remain pharmacodynamic interactions that would warrant avoiding their coadministration.

Pediatric and Geriatric Considerations

The safety and efficacy of indiplon IR or MR in children younger than 18 years have not been established. Compared with young adults, subjects aged 65 years or older showed no statistically significant changes in time to peak plasma concentrations and half-life elimination rates.[17] Based on similar pharmacokinetic profiles, it could be suggested that the same starting dose of indiplon IR or MR be used for adults and geriatric patients. However, despite no statistically significant changes being noted in the pharmacokinetic profiles of geriatric patients studied, there may be unknown pharmacodynamic effects that would warrant initiation of lower starting doses in that population. Indiplon is a central nervous system–active medication, and geriatric patients are often more sensitive to such drugs, compared with younger patients.

Therapeutic and Economic Issues

A lack of statistically significant sleep improvements was reported in a few of the clinical trials with extended study periods. This questions the use of indiplon in chronic treatment of insomnia. Moscovitch et al.[36] tried to clarify this issue with a small, open-label study reporting an 81% improvement in sleep quality at 6 months. Further studies are needed to clarify whether the improvements in sleep parameters allow for chronic, long-term use of indiplon. No published studies have analyzed the potential economic impact of indiplon in clinical practice. The cost of indiplon IR or MR is not known at this time. It could be anticipated to be in a range similar to that of other NSHs. Zolpidem tartrate became the first FDA-approved NSH to become generically available (April 23, 2007) in the US, and the financial implication as it relates to all other available NSHs has yet to be fully determined.[44] Medicare Part D prescription coverage is important to assess with any new FDA-approved sleep medication. Currently, generic zolpidem tartrate is the only NSH consistently listed in tier 1 (generic copay) for most Medicare Part D plans. If marketed, indiplon will most likely fall under the category of tier 3 (nonpreferred brand copay) or nonformulary based on the listing of other trade-name NSHs being considered tier 3 or nonformulary by most Medicare Part D prescription plans.[45]

Dosage and Administration

New Drug Applications have been filed for indiplon IR 5- and 10-mg capsules. In published clinical trials evaluating the efficacy of indiplon IR, doses ranging from 5 to 30 mg have been studied. Indiplon MR formulations that have been studied in published clinical trials have evaluated doses ranging from 10 to 40 mg. Indiplon had not yet received FDA approval at the time of writing.

Place in Therapy

At the time of writing, there had been no efficacy trials comparing indiplon with any of the other NSHs. Indiplon has shown that it is an effective medication to improve both sleep onset and sleep maintenance when compared with placebo. Indiplon's place in the management of insomnia will be based on future trials that will be focused on meeting the recent request of the FDA for more clinical trial data comparing it with insomnia products currently marketed in the US.

Summary

Both the indiplon IR and MR formulations have proven to be effective in a variety of sleep parameters for the treatment of chronic insomnia, when compared with placebo. Limited clinical trial data exist with indiplon in a true transient insomnia patient population. Both adult and elderly populations have been studied in clinical trials, with no major adverse effects noted. Based on recent FDA requests, clinical trial data assessing direct comparisons of indiplon IR with other FDA-approved NSHs are needed to clearly define whether clinical differences exist among these agents. If approved by the FDA, indiplon IR and MR will most likely be used for patients who have trouble with sleep onset and sleep maintenance.

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Indiplon: Un Sedante Hipnótico no Perteneciente a las Benzodiacepinas para el Tratamiento del Insomnio

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EXTRACTO

OBJETIVO: Revisar la farmacología, la farmacocinética, la farmacodinámica, los datos de eficacia, y los efectos adversos de indiplon en el tratamiento de insomnio pasajero o crónico en adultos y pacientes geriátricos.

FUENTES DE DATOS: Una búsqueda de la literatura se llevó a cabo usando MEDLINE (1966–mayo 2008), *Abstractos Farmacéuticos Internacionales* (1970–mayo 2008), y la base de datos Cochrane (2007) para las claves indiplon o NBI-34060. Las referencias citadas en los artículos fueron revisadas para información adicional. Los datos de extractos fueron incluidos sólo en la ausencia de datos significativos publicados.

SELECCIÓN DE ESTUDIOS Y EXTRACCIÓN DE DATOS: Literatura en lenguaje inglés reportando estudios en animales y estudios clínicos en humanos fueron revisados para evaluar la farmacología, la farmacocinética, la farmacodinámica, los datos de eficacia, y los efectos adversos de indiplon. Los ensayos clínicos seleccionados para inclusión fueron limitados a estudios con humanos con la inclusión aceptada de datos de farmacología en animales.

SÍNTESIS DE DATOS: Indiplon es un sedante hipnótico no perteneciente a las benzodiacepinas que exhibe actividad sedante mediante interacción con el complejo de receptores GABAA. Las formas de dosificación de liberación inmediata (IR) tanto como la de liberación modificada (MR) de indiplon han demostrado mejoría en pacientes con DSM-IV-TR insomnio primario en varias áreas de medidas subjetivas y objetivas de sueño. Específicamente, mejorías en el tiempo total de sueño, latencia a sueño persistente, latencia en quedar dormido, despertar después de quedar dormido, y calidad de sueño han sido observadas en ensayos clínicos. Ensayos evaluando ambas formas IR y MR de indiplon no han identificado ningún efecto adverso serio.

CONCLUSIONES: Indiplon es un sedante hipnótico no perteneciente a las benzodiacepinas y más específicamente un agonista del receptor de benzodicepina que ha sido estudiado clínicamente para el manejo de insomnio pasajero y crónico. Ambas formulaciones, IR y MR, han demostrado ser efectivas en una variedad de parámetros del sueño cuando se comparan a placebo para el tratamiento de insomnio crónico. Existen datos clínicos limitados con indiplon en población "verdadera" de pacientes con insomnio pasajero. Basados en peticiones recientes por el FDA de datos clínicos evaluando comparaciones directas entre indiplon IR y otros sedantes hipnóticos aprobados no pertenecientes a las benzodiacepinas se necesita definir claramente las diferencias entre estos agentes.

Traducido por Sonia I Lugo

L'Indiplon: Un Sédatif non Benzodiazépine Hypnotique dans le Traitement de l'Insomnie

JC Marrs

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RÉSUMÉ

OBJECTIF: Analyser le profil pharmacologique, la pharmacocinétique, la pharmacodynamique, les données d'efficacité, et les effets secondaires de l'indiplon dans le traitement de l'insomnie transitoire et chronique chez l'adulte et les patients gériatriques.

REVUE DE LITTÉRATURE: Une recherche bibliographique MEDLINE (1966–mai 2008), *International Pharmaceutique Résumé* (1970–mai 2008), et base de données Cochrane a été effectuée à l'aide des termes clés: indiplon ou NBI-34060. Les références citées dans les articles ont été revues comme additionnelles informations. Les résumés d'information ne furent inclus qu'en absence d'informations importantes publiées.

SÉLECTION DES ÉTUDES ET SÉLECTION DE L'INFORMATION: Des publications en langue anglaise rapportant des études cliniques contrôlées chez l'homme et l'animal ont été analysées afin d'évaluer le profil pharmacologique, la pharmacocinétique, la pharmacodynamique, les données d'efficacité, et les effets secondaires de l'indiplon. Les essais cliniques sélectionnés pour inclusion ont été limités à ceux effectués chez l'homme, avec également une inclusion des données pharmacologiques chez l'animal.

RÉSUMÉ: L'indiplon est un sédatif non benzodiazépine hypnotique qui manifeste son activité sédative via son interaction avec le complexe Gaba-A récepteur. Les préparations de l'indiplon:indiplon à libération immédiate mais également l'indiplon à libération modifiée ont montré des améliorations chez les patients avec des insomnies primaires (critères du DSM-IV-TR) dans différents domaines de mesures subjectives et objectives du sommeil. Des améliorations dans le temps de sommeil total, dans la latence jusqu'au sommeil profond, dans la latence jusqu'au début du sommeil, dans la durée du réveil après induction, et dans la qualité du sommeil ont été particulièrement notées lors des essais cliniques. Les essais évaluant l'indiplon à libération immédiate et modifiée n'ont jusqu'à présent identifié aucun effet secondaire grave.

CONCLUSIONS: L'indiplon est un sédatif non benzodiazépine hypnotique et plus particulièrement un agoniste des récepteurs aux benzodiazépines qui a été cliniquement étudié dans la prise en charge de l'insomnie transitoire et chronique. Les 2 formulations (libération immédiate et modifiée) ont mis en évidence une efficacité dans une variété de paramètres de sommeil en comparaison au placebo pour le traitement de l'insomnie chronique. Des informations limitées sur les essais cliniques avec l'indiplon existent chez une vraie population de patient souffrant d'insomnie transitoire. Basées sur de récentes demandes émanant de la FDA, des informations sur des essais cliniques évaluant des comparaisons directes de l'indiplon avec d'autres sédatifs hypnotiques non benzodiazépines approuvés par la FDA sont nécessaires afin de définir les différences entre ces agents.

Traduit par Thierry Youmbi