

# ZolpiMist™: a new formulation of zolpidem tartrate for the short-term treatment of insomnia in the US

David N Neubauer

Department of Psychiatry, Johns Hopkins University School of Medicine, Baltimore, MD, USA

**Abstract:** ZolpiMist™ is an oral spray formulation of the hypnotic compound zolpidem that was approved by the US Food and Drug Administration in 2008 with an indication for the short-term treatment of insomnia characterized by difficulty with sleep initiation. It was developed by NovaDel Pharma, Inc. using their patented NovaMist™ spray technology. The recommended doses are 10 mg for adults and 5 mg for elderly and debilitated patients to be taken once daily immediately before bedtime. Each metered spray contains 5 mg of zolpidem. ZolpiMist was approved through the 505(b)(2) pathway, which allowed reference to pre-existing efficacy and safety data for the equivalent doses of zolpidem immediate-release tablets. Bioequivalence and pharmacokinetic characteristics were demonstrated in clinical studies with healthy adult and elderly subjects. ZolpiMist is being investigated for the possible indication of use during middle-of-the-night awakenings when the patient has at least 4 hours available to remain in bed.

**Keywords:** ZolpiMist, zolpidem, oral spray formulation, hypnotic, insomnia

Insomnia represents difficulty falling asleep or remaining asleep, or poor quality sleep, when one has the opportunity to be sleeping. Insomnia may be diagnosed as a disorder when the sleep disturbance is associated with daytime consequences, such as fatigue, concentration or memory impairment, irritability, daytime sleepiness, or reduced energy, motivation, or initiative.<sup>1</sup> The nighttime symptoms of insomnia occur in about 30% to 40% of the general population and approximately 5% to 10% of individuals meet the diagnostic criteria for an insomnia disorder. Although insomnia often occurs transiently, the sleep difficulty commonly evolves into a chronic condition. The etiology of insomnia typically is multifactorial and comorbid conditions often are present. Persistent insomnia is associated with an elevated future risk of various disorders, most prominently mood and anxiety disorders.<sup>2,3</sup>

Evidence-based treatments for insomnia include cognitive behavioral therapy (CBT) and pharmacotherapy.<sup>3</sup> Medications approved by the US Food and Drug Administration (FDA) for the treatment of insomnia include various benzodiazepine receptor agonist (BZRA) hypnotics, a selective melatonin receptor agonist (ramelteon), and a low-dose formulation of a selective histamine H<sub>1</sub> receptor antagonist (doxepin). The BZRA hypnotics available in the US include the older compounds incorporating a benzodiazepine structure (estazolam, flurazepam, quazepam, temazepam, and triazolam) and the newer non-benzodiazepine compounds (eszopiclone, zaleplon, zolpidem, and zolpidem extended-release). All of these compounds are positive allosteric modulators of GABA responses at the pentameric GABA<sub>A</sub> receptor complex, where a benzodiazepine

Correspondence: David N Neubauer  
Johns Hopkins Bayview Medical Center,  
4940 Eastern Avenue, Box 151, Baltimore,  
MD 21224, USA  
Tel +1 410-550-0066  
Email neubauer@jhmi.edu

recognition site exists at the interface of  $\alpha$  and  $\gamma$  subunits. GABA is a widespread inhibitory neurotransmitter and enhancing its activity promotes a sedating effect.<sup>4</sup> The BZRA hypnotics vary according to their elimination half-lives (ranging from 1 hour to several days) and corresponding durations of action. The non-benzodiazepine hypnotics tend to have improved safety and tolerability profiles compared with the benzodiazepines, in part because of their generally shorter elimination half-lives. There may be additional benefits related to the greater  $\alpha_1$  subunit subtype selectivity of the non-benzodiazepines. In addition to the FDA approved medications, patients may be prescribed a wide variety of sedating medications (eg, antidepressants and antipsychotics) on an off-label basis, or they may use melatonin, dietary supplements, herbal preparations, or over-the-counter antihistamines in the attempt to improve their sleep.

Zolpidem initially became available in France in 1988 with the brand name Stilnox<sup>®</sup> and then in the US in 1993 as Ambien<sup>®</sup>. For many years it has been the most widely prescribed hypnotic both in the US and internationally. An extended-release formulation (Ambien CR<sup>®</sup>) was first marketed in the US in 2005 and it remains under patent protection. The US patent for the immediate-release zolpidem tablet expired in 2007 and generic tablet versions immediately became available. The extended-release formulation is a dual-layer pill incorporating both immediate- and delayed-release components which modestly extend the pharmacokinetic profile to enhance sleep maintenance. Although the two zolpidem formulations have the identical active ingredient, their FDA approved indications differ with regard to the recommended duration of use. Immediate-release zolpidem retains the original indication for the short-term treatment of insomnia, while the extended-release zolpidem formulation has no implied duration of use limitation in the indication. Additionally, the immediate-release zolpidem indication relates to sleep onset difficulty, while the extended-release formulation includes difficulty with sleep onset or sleep maintenance.

Over the past several years alternate delivery formulations of non-benzodiazepine hypnotics have been investigated. These have included oral spray, nasal spray, sublingual tablet, oral dissolvable, and inhalation systems. At the time of this writing, the FDA has approved two alternative delivery formulations of immediate-release zolpidem and others remain in development. The two alternative delivery zolpidem products currently approved in the US are Edluar<sup>®</sup>, a sublingual tablet marketed by Meda Pharmaceuticals, Inc. and ZolpiMist<sup>™</sup>, an oral spray formulation developed by NovaDel Pharma, Inc (Flemington, NJ, USA). This article

will review the development and available clinical data for ZolpiMist.

## ZolpiMist

ZolpiMist is a zolpidem oral spray formulation developed by NovaDel Pharma, Inc, a pharmaceutical company specializing in the creation of oral spray formulations of various medications. In 2004 NovaDel announced plans to investigate a lingual spray zolpidem formulation using their patented NovaMist<sup>™</sup> delivery technology. The company suggested that the oral spray delivery would promote a “more rapid onset of therapeutic activity,” limit the first-pass hepatic effects associated with gastrointestinal absorption, and represent a convenient product that does not require water and that a patient could self-administer “as they would a breath freshener.”<sup>5</sup> NovaDel has an FDA-approved nitroglycerin oral spray product (NitroMist<sup>™</sup>) for angina pectoris, and is investigating oral spray medication formulations for nausea and vomiting, pre-procedure anxiety, and erectile dysfunction.

NovaDel pursued regulatory approval of ZolpiMist through the US FDA 505(b)(2) pathway, which was created to encourage drug development innovation while limiting requirements for the duplication of preclinical and clinical studies of previously approved medications. This less costly and streamlined approach permits a new drug application to reference published literature and previous FDA safety and effectiveness findings. New drug applications that may be appropriate for 505(b)(2) consideration include changes in the dosage form, strength, and route of administration, and with the substitution of an active ingredient in a combination product. The new drug application only requires new investigations related to the specific change from the approved drug. Accordingly, lengthy and costly duplicate safety and efficacy studies may not be necessary.<sup>6</sup>

Since NovaDel did not request any changes related to the dosage strength or indications for ZolpiMist, new studies required for FDA 505(b)(2) submission were quite limited and primarily involved pharmacokinetics with healthy subjects to demonstrate bioequivalence. Additional data related to process validation and registration stability batches produced at the intended manufacturing facility.<sup>7,8</sup> There have been no efficacy studies of sleep parameters with healthy or insomnia subjects, and there have been only minimal pharmacodynamic and safety assessments with the oral spray formulation. Most available data on ZolpiMist has been presented in NovaDel press releases.

In December, 2008, the FDA approved ZolpiMist 5 mg and 10 mg doses for the short-term treatment of insomnia

characterized by difficulties with sleep initiation. This indication represents the identical wording as that for immediate-release zolpidem. The details of the ZolpiMist approved label also are nearly identical to that of immediate-release zolpidem, except for those items specifically relating to the oral spray administration.<sup>9,10</sup>

In November 2009, NovaDel reported receiving a United States Patent and Trademark Office Notice of Allowance regarding US Patent Application 10/671,715 (Buccal, Polar and Non-polar Spray Containing Zolpidem), which includes claims related to the use of the NovaMist oral spray technology in the treatment of insomnia. The company noted that, once issued, the patent will expire in 2018.<sup>11</sup> NovaDel announced in December 2009 that the application was approved and issued as US Patent, No. 7632517.<sup>12</sup>

In November, 2009, NovaDel announced signing an exclusive license and distribution agreement with ECR Pharmaceuticals Company, Inc., a subsidiary of Hi-Tech Pharmacal Co., Inc. for the commercialization and manufacture of ZolpiMist in the US and Canada. According to the agreement, ECR will be responsible for manufacturing and marketing ZolpiMist, and will pay NovaDel US\$3 million, 15% royalties, and possible additional milestone payments.<sup>13</sup>

In addition to the current ZolpiMist indication for the treatment of insomnia characterized by sleep onset difficulty, NovaDel is investigating the use of low-dose zolpidem in an oral spray formulation to be taken during middle-of-the-night awakenings with difficulty returning to sleep. If approved, a dose might be taken if the patient still has at least four hours remaining available for sleep. The current ZolpiMist dosing guidelines state that it should be used only if the patient is able to stay in bed for a full night (7–8 hours) before he or she must be active again.<sup>10</sup>

## ZolpiMist characteristics

ZolpiMist is an oral formulation of zolpidem tartrate designed to be administered as a spray in the mouth on the tongue. The solution is a clear, slightly yellowish cherry flavored liquid. The medication will be provided in a child-resistant container including an amber glass bottle with a metered spray pump assembly designed to deliver 5 mg of zolpidem tartrate (100 µL) per spray. Accordingly, one actuation will provide a 5 mg dose and two actuations will give a 10 mg dose. One bottle should supply 60 metered actuations after an initial 5 priming sprays. (Further priming may be necessary if the pump is not used for 14 days.) Inactive ingredients include artificial cherry flavor, benzoic acid, citric acid monohydrate,

hydrochloric acid, neotame, propylene glycol, and purified water. ZolpiMist is manufactured by the Swedish company Rechon Life Sciences AB.<sup>10</sup>

## ZolpiMist pharmacokinetic studies

NovaDel reported that no significant differences were found between oral mucosal and gastrointestinal absorption in an investigation of zolpidem metabolites involving plasma samples drawn from 12 subjects given 5 and 10 mg zolpidem oral spray and 5 and 10 mg zolpidem tablets in a crossover design. Plasma samples were taken immediately prior to dosing, after 5, 10, 15, 20, 30, 45, 60, and 90 minutes, and after 2, 3, 4, 6, 8, 10 and 12 hours postdose. The four zolpidem metabolites that were measured had higher  $C_{max}$  levels following 10 mg zolpidem tablet ingestion compared with 10 mg oral spray administration, a finding attributed to the entire tablet dose being exposed to hepatic first-pass metabolism. The metabolic ratios of the major zolpidem metabolite for oral spray 5 and 10 mg to the 10 mg tablet were 0.841 and 0.854, respectively.<sup>14</sup>

The effect of food on ZolpiMist pharmacokinetics was assessed in a study of 14 healthy male subjects ages 18 through 45 years administered zolpidem oral spray following a fast of at least 8 hours or 5 minutes following a standard high-fat meal. Compared with the fasting values, ZolpiMist given after the meal was associated with a 27%  $AUC_{0-\infty}$  decrease and a 58%  $C_{max}$  decrease, as well as a 225%  $T_{max}$  prolongation from 0.8 to 2.6 hours.<sup>10</sup>

A linear ZolpiMist dose relationship with  $C_{max}$  and  $AUC_{0-\infty}$  was demonstrated in a single-dose crossover study of 10 healthy male subjects aged 18 to 40 years who were administered 2.5, 5, and 10 mg.<sup>10</sup>

The bioequivalence of ZolpiMist and zolpidem tablets was demonstrated in a four-way crossover study with adults given 5 and 10 mg doses of the oral spray and tablet formulations, and also in a two-way crossover study with older adults given 5 mg doses of each formulation. The adult study was performed with 43 healthy male and female subjects ages 18 to 45 years. The respective  $C_{max}$  mean values for 5 and 10 mg ZolpiMist doses were 114 (range, 19 to 197) and 210 ng/mL (range, 77 to 401). This compares with the respective zolpidem tablet 5 and 10 mg  $C_{max}$  mean values of 123 (range, 53 to 221) and 219 ng/mL (range, 101 to 446). The mean  $T_{max}$  for both ZolpiMist doses was approximately 0.9 hours, while the 5 and 10 mg zolpidem tablets had  $T_{max}$  values of 0.9 and 1.0 hours, respectively. The mean zolpidem  $t_{1/2}$  values associated with ZolpiMist 5 and 10 mg administration were 2.7 (range, 1.7 to 5.0) and 3.0 hours (range, 1.7 to

8.4), respectively. The zolpidem  $t_{1/2}$  values resulting from the 5 and 10 mg zolpidem tablet doses were 2.8 (range, 1.5 to 6.0) and 3.1 hours (range, 1.1 to 8.6), respectively.<sup>10,15</sup>

Pharmacokinetic analyses of the adult bioequivalence study assessed the time to reach the standard zolpidem therapeutic drug concentration of 20 ng/mL. This level was reached within 15 minutes following ZolpiMist 5 and 10 mg administration in 65% and 79% of the subjects, respectively. This corresponds to 19% and 26% of the subjects reaching this therapeutic level within 15 minutes following 5 and 10 mg zolpidem tablet dosing.<sup>15</sup>

The older adult bioequivalence study with the 5 mg oral spray and tablet doses was performed with 24 healthy subjects ages 65 years and greater (mean age 71.9 years). The ZolpiMist mean  $C_{max}$  and  $AUC_{0-\infty}$  values were 134 ng/mL and 493 ng\*hr/mL, respectively.<sup>10,15</sup>

## ZolpiMist pharmacodynamic studies

Efficacy claims for ZolpiMist rely entirely on the preexisting literature supporting the sleep enhancing effects of immediate-release zolpidem. Although no sleep parameters have been assessed in the clinical studies of ZolpiMist, a pharmacodynamic component was incorporated into the adult bioequivalence study with the use of the Digit Symbol Substitution Test (DSST) as a surrogate for sedation. A decline from baseline performance on the DSST following medication dosing may reflect the sedating effect. NovaDel reported that when subjects were given ZolpiMist 10 mg they demonstrated a fourfold greater reduction in DSST scores at the 13 minute post-dose assessment compared with when given the 10 mg zolpidem tablet. With the 5 mg ZolpiMist dose the DSST reduction was twofold when compared with either the 5 mg or 10 mg zolpidem tablet doses.<sup>15</sup>

## ZolpiMist contraindications, warnings and precautions, adverse reactions, and drug interactions

The FDA approved labeling for these sections mirrors the content for immediate-release zolpidem tablets and is similar for other benzodiazepine receptor agonist hypnotics; none are specific for ZolpiMist or were derived from the ZolpiMist clinical studies. The only contraindication is hypersensitivity to zolpidem tartrate. The highlights of prescribing information warnings and precautions include the need to evaluate for comorbid diagnoses after 7 to 10 days of use; severe anaphylactic and anaphylactoid reactions; abnormal thinking, behavioral changes, and complex behaviors (eg,

“sleep-driving” and hallucinations); depression; the recommendation to prescribe the least amount feasible to avoid intentional overdose; possible withdrawal effects with rapid dose reduction or discontinuation; CNS-depressant effects (eg, impaired alertness and motor coordination), especially when combined with other CNS depressants, including alcohol; the recommendation for a lower dose in elderly or debilitated patients; and caution with close monitoring in patients with hepatic impairment, mild to moderate COPD, impaired drug metabolism or hemodynamic responses, and mild to moderate sleep apnea.<sup>10</sup>

The most commonly observed adverse reactions for short-term use were drowsiness, dizziness, and diarrhea and for long-term use were dizziness and drugged feelings.<sup>10</sup> The highlighted potential drug interactions include CNS depressants, imipramine, chlorpromazine, rifampin, and ketoconazole. For use in special populations, it is noted that based on animal data zolpidem can cause fetal harm (Pregnancy Category C), there may be infant exposure via breast milk, and safety and effectiveness have not been established in pediatric use.<sup>10</sup>

All formulations of zolpidem and other benzodiazepine receptor agonist hypnotics are classed as Schedule IV controlled substances by the US Drug Enforcement Agency due to their relatively low potential for abuse and dependence. The ZolpiMist FDA approved labeling suggests that careful monitoring should be performed when zolpidem is prescribed for people with a history of abuse of, or addiction to, drugs or alcohol.

## Commentary

NovaDel has developed an oral spray zolpidem formulation for which it has been granted patent protection and approval by the US FDA for the treatment of insomnia with an indication nearly identical to immediate-release zolpidem tablets. The only new studies required for the FDA approval have related to bioequivalence and manufacturing. Consequently, there are no sleep-related efficacy and minimal safety data specific to ZolpiMist. Clinical experience will be necessary to assess the actual advantages and disadvantages of this rather novel approach in the pharmacotherapy of insomnia.

NovaDel states that their proprietary NovaMist delivery system allows sublingual, buccal, and gingival absorption of medications with advantages possibly including faster onset of action, lower dose requirement, enhanced patient compliance and convenience, avoiding the need to swallow or drink a liquid, increased bioavailability with the bypass of hepatic metabolism, and avoidance of the variable GI absorption

due to food.<sup>16</sup> While these features may be advantageous for a hypnotic medication in certain clinical circumstances, it is not yet established that all of these claims are valid for ZolpiMist.

Certainly the ZolpiMist oral spray delivery bypasses the need for water and swallowing a pill. There may be a benefit in the rapid onset of action suggested by the much greater percentage of subjects reaching a standard therapeutic zolpidem blood level with the oral spray compared with the tablet formulation. On the other hand, there may be an increased risk for the faster onset of potential side effects, such as amnesia or ataxia. However, the nearly identical zolpidem  $T_{max}$  values for the oral spray and tablet formulations raise the question of whether there will be a significant clinical difference between the two formulations. Although NovaDel emphasizes the oral absorption, a considerable amount of the ZolpiMist absorption may actually occur in the stomach, as suggested by the marked pharmacokinetic effects associated with the use of the oral spray following a standard high-fat meal. Whether the oral spray delivery will allow a lower dose also remains to be established, as the bioequivalence studies by necessity compared equal oral spray and tablet doses.

Along with possible benefits, might the use of an oral spray hypnotic be associated with unique risks? Presumably there will be little variability in the dose in each spray once the pump priming has been performed. However, there may be a greater chance for bedtime confusion with the sprays compared with pills taken at the bedside. The oral spray also might facilitate accidental or intentional overdose, and could represent a desirable route for abuse.

Since NovaDel employed the 505(b)(2) pathway in the FDA approval application for ZolpiMist, the company depended on the current zolpidem immediate-release tablet efficacy and safety data. Accordingly, the ZolpiMist indication and approved labeling essentially mirrors that of zolpidem tablets, including the reference only for the treatment of insomnia with sleep-onset difficulty and the recommendation for short-term use. This is in contrast to the broader zolpidem extended-release indication for sleep onset or maintenance and the absence of an implied limitation on the duration of use.

One particular potential advantage for a convenient, rapid-onset, and relatively short-acting hypnotic would be use during middle-of-the-night awakenings, as long as the patient has several more hours available for sleep. Currently no medications have specific indications for use during the nighttime to facilitate a return to sleep; all are intended

for bedtime use for difficulty falling asleep or maintaining sleep. If a patient has no difficulty falling asleep but does have difficulty returning to sleep upon middle-of-the-night awakenings, a reasonable plan would be using an appropriate hypnotic at that time on an as-needed basis. As noted above, NovaDel currently is investigating the use of ZolpiMist for middle-of-the-night awakenings with the hope that this may represent a future indication.<sup>17</sup> However, gaining FDA approval for a middle-of-the-night dosing indication will be challenging for any hypnotic formulation due to the burden of proving the absence of impairment or excessive sleepiness just a few hours following the dose. Further, any indication or dosage changes likely will require new efficacy clinical trials.

ZolpiMist comes to the US marketplace with abundant generic zolpidem tablet competition, numerous other branded and generic FDA-approved hypnotics, and other branded alternate delivery oral formulations with similar potential advantages that either have been approved by or currently are being evaluated by the FDA. While ZolpiMist's oral spray delivery certainly is unique for a hypnotic, the extent to which it represents a major clinical advance remains to be seen.

## Disclosure

Dr Neubauer has served as a consultant to McNeil Consumer Products, Takeda Pharmaceuticals, and sanofi-aventis.

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