ZOLMITRIPTAN NASAL SPRAY

PROTOCOL NO. IPX229-B16-01

A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, CROSSOVER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ZOLMITRIPTAN NASAL SPRAY FOR THE TREATMENT OF ACUTE MIGRAINE IN SUBJECTS AGES 6 TO 11 YEARS, WITH AN OPEN-LABEL EXTENSION

SPONSOR

Impax Laboratories, Inc.,

acting through its Impax Specialty Pharma division (Impax)

[redacted]

Hayward, CA 94544

Original Protocol, 24 October 2016

CONFIDENTIALITY STATEMENT

SIGNATURE PAGE

Reviewed and approved by:

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Date

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Date

INVESTIGATOR'S AGREEMENT

Protocol No.: IPX229-B16-01

Protocol Title: A Multicenter, Randomized, Double-blind, Placebo-controlled, Crossover Study to Evaluate the Efficacy and Safety of Zolmitriptan Nasal Spray for the Treatment of Acute Migraine in Subjects Ages 6 to 11 Years, with an Open-Label Extension

I have read this protocol and agree to conduct the study as outlined herein, complying with the obligations and requirements of clinical investigators and all other requirements of International Conference on Harmonization (ICH), Good Clinical Practice (GCP), and the appropriate regulatory authority.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this clinical study. I will discuss this material with them to ensure that they are fully informed regarding the study medication, the conduct of the study, and the obligations of confidentiality.

_____ _____

Principal Investigator's signature Date

_____

Principal Investigator's printed name

STUDY CONTACT INFORMATION

Changes in Impax study personnel listed on this page do not require a protocol amendment.

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1. SYNOPSIS

Name of Sponsor/Company: Impax Laboratories, Inc.(Impax), [redacted]., Hayward, CA 94544 on behalf of AstraZeneca PLC
Name of Investigational Product: Zolmitriptan Nasal Spray (ZNS)
Name of Active Ingredient: Zolmitriptan
Protocol Title: A Multicenter, Randomized, Double-blind, Placebo-controlled, Crossover Study to Evaluate the Efficacy and Safety of Zolmitriptan Nasal Spray for the Treatment of Acute Migraine in Subjects Ages 6 to 11 Years, with an Open-Label Extension
Protocol No: IPX229-B16-01
Study center(s): Multiple study sites in the USA
Phase of development: 3
Objectives: To evaluate the efficacy and safety of zolmitriptan nasal spray (ZNS) in the acute treatment of migraine headache in subjects ages 6 to 11 years.
Methodology: This is a randomized, double-blind, placebo-controlled, 2-period, crossover outpatient study. Within 2 weeks of screening, eligible subjects will return to the study site to begin a 6-week single-blind run-in period, during which a single migraine headache will be treated with 1 dose of placebo. Subjects will be instructed to treat a headache of moderate or severe pain intensity within approximately 20 minutes of onset of headache pain reaching moderate or severe intensity and to complete a diary capturing the headache severity using a 4-point headache pain intensity scale (severe = 3, moderate = 2, mild = 1, or no pain = 0), other associated symptoms, and use of rescue medication(s). Headaches occurring while the child is at school will not be treated with study drug. Adverse events (AEs) will also be collected. Diary entries are recorded prior to treatment with study drug, at 30 minutes and at 1, 2, and 24 hours after treatment. If, after 2 hours, the migraine headache has not responded (ie, reduced to a pain intensity of mild or no pain), the subject is permitted to use approved rescue medication(s). Any subsequent migraine episodes during the run-in period will be treated with the subject's protocol-allowed pre-study acute migraine medication. Subjects who have not treated a migraine headache with blinded placebo during the 6-week run-in period will be considered screen failures. Placebo challenge responders (defined as those subjects who treat a migraine attack of moderate (2) or severe (3) intensity and who achieve a mild (1) or no pain (0) response within 2 hours after dosing) will be discontinued from the study. Eligible placebo non-responders will be randomized to one of two treatment sequences within their respective body weight stratum determined immediately prior to randomization: ZNS followed by placebo, or placebo followed by ZNS. Subjects weighing less than 50 kg will be allocated randomly to receive ZNS 2.5 mg or 1 mg in a 5:1 fashion during the ZNS treatment. Subjects weighing at least 50 kg will be allocated randomly to receive ZNS 5 mg or 2.5 mg in a 5:1 fashion during the ZNS treatment. Following randomization, subjects will have up to 6 weeks to treat a migraine attack of moderate or severe intensity. During each treatment period, subjects will treat a moderate to severe migraine attack within approximately 20 minutes of the headache pain reaching moderate or severe intensity. Headaches occurring while the child is at school will not be treated with study drug. Headache pain intensity is assessed by the subjects at 30 minutes and at 1, 2, and 24 hours post-dose using a subject diary with a 4-point headache pain intensity scale. The primary efficacy variable is headache pain intensity at 2 hours based on data from subjects treated with the higher dose in each

weight stratum. Subjects who do not obtain satisfactory relief of migraine pain by 2 hours after taking study drug are permitted to treat the migraine with their protocol-allowed pre-study acute migraine medication (eg, nonsteroidal anti-inflammatory drugs [NSAIDs] or acetaminophen) at that time or at any time thereafter, if the headache does not resolve or if it recurs, with the exception that all triptans and ergot derivatives are prohibited for 24 hours following the last dose of study drug. After treating a migraine attack in the first treatment period, the subject will return to the study site for the second treatment period study drug. Subjects will then have up to 6 weeks to treat a second migraine attack. Subjects who successfully complete the double-blind portion of this study and are eligible will be offered participation in a 6-month outpatient open-label safety extension (OLE) where they will treat up to 4 migraine attacks per month with ZNS. Headaches occurring while the child is at school will not be treated with study drug. During the OLE, subjects will be assessed for pain-free status at 2 hours and for migraine-associated disability.
Number of subjects (planned): Approximately 393 subjects will be enrolled to randomize 264 so that at least 180 subjects will complete both double-blind treatment periods. With the 5:1 (high dose:low dose) randomization ratio for each of the 2 weight strata, it is estimated that 150 high-dose subjects will complete both double-blind treatment periods and 30 subjects randomized to the low dose level will complete both double-blind treatment periods. Approximately 100 subjects who complete the double-blind crossover phase will enter the 6 month OLE to enable at least 50 subjects to complete at least 6 months treating on average at least one migraine attack per month (treating up to 4 migraine attacks per month) with ZNS.
Diagnosis and main criteria for inclusion: • Each child must have a responsible trained adult with knowledge of the conduct of the study who must be available to supervise migraine treatment and study requirements. • Parent or legal guardian is able to provide written informed consent and subject is able to provide written assent. • Subjects ages 6 to 11 years at the time of screening; subjects must not be enrolled if they will turn 12 years of age within 14 weeks after randomization. • An established diagnosis of migraine (history indicating the presence of migraine for at least 6 months) with or without aura as defined by the International Headache Society revised criteria (ICHD-3B). • By history, average migraine frequency of ≥ 2 attacks per month of moderate or severe intensity lasting on average ≥ 3 hours per attack untreated and not experiencing satisfactory relief with NSAIDs or acetaminophen. • By history, migraine attacks typically occur at intervals of >24 hours apart. • By history, has at least 16 headache-free days per month on average, for 3 months before Screening. • Has the ability to differentiate between migraine and non-migraine headaches.
Investigational product, dosage and mode of administration: Zolmitriptan Nasal Spray (ZNS) 1 mg, 2.5 mg, and 5 mg. ZNS placebo.
Study Duration: • Part 1: Up to 20 weeks (including Screening, placebo-challenge, and double-blind treatment) • Part 2: Up to 6 months of OLE following successful completion of Part 1

Criteria for evaluation:

Efficacy Double-blind:

- Primary: Proportion of subjects who achieve pain-free status at 2 hours based on data from subjects treated with the high dose from each stratum. "Pain-free" is defined as a reduction from moderate (2) or severe (3) pain to no (0) pain.
- Secondary: All endpoints will be summarized by the proportion of subjects (except time to use of rescue medication) treated with the high and low dose levels.
    - Pain-free status at 2 hours post-dose for the low dose level
    - Pain-free status at 30 minutes and at 1 and 24 hours post-dose
    - Absence of associated migraine symptoms (photophobia, phonophobia, nausea) at 30 minutes and at 1, 2, and 24 hours post-dose.
    - Headache response – defined as a reduction from moderate (2) or severe (3) pain to mild (1) or no (0) pain at 30 minutes and at 1, 2, and 24 hours post-dose.
    - Incidence and time to use of rescue medication up to 24 hours post-dose.
    - Headache recurrence rates 2 to 24 hours post treatment for the subset of subjects who attained a 2-hour pain-free and/or a 2-hour headache response and who don't use any rescue medication.
    - Sustained headache response and sustained pain free response 2 to 24 hours post-dose
- Clinical Assessments: OLE
    - Proportion of subjects who report pain-free status at 2 hours for each migraine attack that reaches moderate or severe intensity and is treated with the study drug.
    - PedMIDAS at randomization and end of OLE.

Safety:

Adverse events, clinical laboratory tests, 12-lead electrocardiograms (ECGs), vital signs, and physical examinations, and assessment of suicidality.

Statistical methods:

Sample size:

In this crossover trial, 150 subjects treated with one of the high doses (2.5 mg in the low weight stratum and 5 mg in the high weight stratum) completing both treatment periods will be adequate to detect a difference of 0.11 in the percentage of subjects who are pain free at 2 hours between ZNS and placebo assuming a standard deviation of 0.4 with at least 90% power using a 2-tailed test (α=0.05). Additionally, approximately 30 subjects will be treated with one of the low doses (1 mg in the low weight stratum and 2.5 mg in the high weight stratum) to provide information on lower doses.

Analysis methods:

The analysis will be conducted separately for each of the two dose levels (high, low).

The high dose will be compared to placebo at a 5% level of significance. Subjects treated with one of the high doses (2.5 mg in the low weight stratum and 5 mg in the high weight stratum) who complete both treatment periods will be included in the primary statistical analysis comparing ZNS to placebo. The primary endpoint, pain-free status at 2 hours, will be analyzed using generalized estimating equations methods. The model will include treatment, period, weight, and baseline headache pain intensity. The results of the analysis will be presented in terms of odds ratio for the treatment effect and the corresponding 95% confidence interval. This method will also be used to analyze the pain-free status at other time points, absence of associated migraine symptoms (photophobia, phonophobia, nausea) and any other binary response variables, eg, headache response, subjects requiring rescue

medication(s), headache recurrence rate, sustained headache response and sustained pain free response.

The data from the low dose level will be summarized to determine if the results are consistent with the high dose level results. Additionally, analysis methods for the low dose level will be similar to the ones used for the high dose group.

Time to use of rescue medication(s) for the two treatments will be compared at each attack using the Cox Proportional Hazards model with the effects of treatment, and baseline headache pain intensity in the model. Time to use of rescue medication will be graphically summarized using the Kaplan-Meier estimation.

All comparisons of secondary endpoints will be tested at 5% significance level without any multiplicity correction.

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse event
AR	adverse reaction
CMH	Cochran-Mantel-Haenszel
C-SSRS	Columbia–Suicide Severity Rating Scale
DHE	dihydroergotamine
ECG	electrocardiogram
EOS	end of study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEE	Generalized Estimating Equations
HIPAA	Health Insurance Portability and Accountability Act
IAF	Informed Assent Form
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICHD-II	International Classification of Headache Disorders, 2nd edition
ICHD-3B	International Headache Society-revised criteria
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IWRS	Interactive Web and Voice Response System
LOCF	Last observation carried forward
NSAID	nonsteroidal anti-inflammatory drugs
MAO-A	monoamine oxidase-A inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
ODT	orally disintegrating tablets
OLE	open-label safety extension
PedMIDAS	Pediatric Migraine Disability Assessment

Abbreviation or Specialist Term	Explanation
PedsQL 4.0	Pediatric Quality of Life Inventory, version 4.0
PI	Principal Investigator
SAE	Serious adverse event
SNRI	Serotonin–norepinephrine reuptake inhibitors
SSRI	Selective serotonin reuptake inhibitors
ZNS	Zolmitriptan Nasal Spray

4. INTRODUCTION

The prevalence of migraine among individuals aged 12 years and older in the United States (US) is estimated to be approximately 12% (approximately 8% among patients ≤20 years of age) (Abu-Arafeh and Russell 2010, Buse et al 2012, Merikangas 2013, Stewart et al 1992, Stewart et al 1994). The prevalence of migraine increases throughout adolescence, peaks in midlife (ie, age 18 to 49 years), and declines after age 50 (Headache Classification Subcommittee (IHS) 2004, Martin et al 1994, Stewart 1992, Stewart et al 1994). In terms of migraine onset, first experiences of migraines occur most frequently between the ages of 14 and 15 years at 18.8 (95% confidence interval [CI]: 14.7, 24.1)/1000 person-years for females and between 10 and 11 years at 10.1 (95% CI: 7.5, 13.6)/1000 person-years for males (Stewart 1991). Estimates of migraine in children younger than 12 years old in the US are limited; however, the majority of data available from the US, Europe, and Asia suggest that the prevalence of migraine among children younger than 12 years old is low in comparison with adolescents and adults. An epidemiologic study conducted in the 1950's in Sweden of 6000 school-aged children reported that the prevalence of frequent or recurring patterns of headache, of which migraine represents a significant subset, occurred in 2.5% of 7-year-olds and in up to 15% of 15-year-olds (Bille 1962). Using a structured interview survey in 1083 children ages 3 to 11 years who were part of a UK urban general practice, Mortimer et al found that 3.7% had migraine with IHS criteria (Mortimer et al 1992). Using a teacher-directed questionnaire in 2921 Finnish children who started school in 1974, Sillanpaa et al found that 2.7% had migraine at age 7 (Sillanpää 1983). The incidence of migraine peaks earlier in boys than in girls; the mean age of onset is 7 years and 11 years for boys and girls, respectively (Laurell et al 2004).

Migraines can have a significant impact on a child's life. The 1989 National Health Interview Survey found that within a 2-week period, 975,000 children had a migraine, resulting in 164,454 missed school days within this period (Stang and Osterhaus 1993). The Pediatric Migraine Disability Assessment (PedMIDAS) has been developed for children and can be highly effective instrument in assessing the disability of migraine and subsequent treatment outcomes (Hershey et al 2001).

Hershey et al proposed several modifications to the International Classification of Headache Disorders, 2nd edition (ICHD-II) diagnostic criteria for migraine to increase its sensitivity for the diagnosis of childhood migraine (Hershey et al 2005). The characteristics of headache in 260 patients, ages 18 and under, clinically diagnosed with migraine at two large pediatric headache centers were compiled using standard intake questionnaires. Modification of the ICHD-II criteria (ICHD-3B) to include bilateral headache, headache duration of 1 to 72 hours (instead of 4 to 72 hours), and nausea and/or vomiting plus 2 of 5 other associated symptoms (photophobia, phonophobia, difficulty thinking, lightheadedness, or fatigue) in addition to the usual description of moderate to severe pain of a throbbing or pulsating nature worsening or limiting physical activity, improved the sensitivity of migraine diagnosis from 61.9% to 84.4%.

Currently, four triptans are FDA-approved for the treatment of adolescent migraine ages 12 to 17 (almotriptan, rizatriptan, and sumatriptan-naproxen tabs, and zolmitriptan nasal spray [ZNS]) and only one triptan (rizatriptan) is approved for school age children, ages 6 to 11. The approval of rizatriptan was based on the Ho et al study of subjects ages 6 to 17 (Ho et al 2012). A weight-

based dosing approach was used. For the primary endpoint, 2-hour pain free in the age 12 to 17 cohort, the difference in proportions (8.6%) was statistically significant ($p < 0.01$) with an odds ratio of 1.55, but was less than the predefined clinically significant difference of 11%. The 2-hour headache response difference (7.4%) for this age cohort was not significant (OR = 1.35), possibly due to the high placebo response (51.4%). Neither of these endpoints was significant in the age 6 to 11 age group (9.4% and -1.8% differences respectively for the 2-hour pain free and response rates). Multiple pharmaceutical company-sponsored pediatric acute treatment studies have been completed with negative outcomes with triptans that have previously approved to treat adult migraine. For example, Winner et al reported a multicenter, randomized, double-blind, placebo-controlled trial of eletriptan 40 mg in 274 adolescents (Winner 2007). On the primary endpoint (2-hour headache response), there was no significant difference between active and placebo (57% vs. 57%). In fact, there were no significant improvements for any of the outcomes at 1 and 2 hours. The authors concluded that, similar to other studies of triptans in adolescents (Lewis 2005), the high placebo response rates prevented statistical efficacy differentiation from placebo (Lewis 2005, Winner 2007). Interestingly, the FDA has noticed the problems with high placebo rates in pediatric acute migraine triptan trials. In a study conducted by mostly FDA employees, Sun et al reported a systematic review and analysis of trial data to identify possible causes for the failure of multiple pediatric triptan trials (Sun 2013). They observed high placebo response rates consistently across all trials and suggested that these rates represented the principal challenge for pediatric abortive trials; however, they also conceded that the reasons for these high rates "remain speculative." They observed that enrichment with selection of subjects who have longer lasting attacks was by itself insufficient to overcome the high placebo rates. These authors recommended an additional enrichment strategy of non-randomization of patients with an early placebo response rate.

Evers et al analyzed the placebo response rates of 8 crossover and of 11 parallel-group acute treatment childhood and adolescent double-blind randomized published trials and found that the crossover studies were associated with considerably lower placebo-response rates compared with the parallel group studies (2-hour pain-free: 19.2% vs. 27.1%; 2-hour pain relief: 39.4% vs. 56.9%) (Evers 2009). In a second study, Evers reported on the between treatment group difference in proportions in 6 crossover and 11 parallel group trials and showed that the pooled crossover studies data were associated with larger therapeutic gains. The pooled 2-hour (active vs. placebo) responder rates were: pain-free (36.0% vs. 17.7%, and 32.5% vs. 26.3%) in crossover and parallel group studies, respectively; pain relief (67.3% vs. 43.0%, and 61.6% vs. 55.5%) (Evers 2013). All of these pooled active versus placebo comparisons were significant. The author again concluded that pediatric triptan parallel group trials show a very low therapeutic gain because of a high placebo response rate.

Zolmitriptan tablets, zolmitriptan orally disintegrating tablets (ODT), and zolmitriptan nasal spray formulations are FDA-approved to treat acute migraine attacks in adults, and, the nasal spray was recently approved (June 2015) to treat adolescents ages 12 to 17. In adults, ZNS 5 mg is significantly effective versus placebo on the headache response and pain-free response rates at all time points between 30 minutes and 4 hours, inclusive, including the 2-hour primary endpoint. The ZNS 2.5 mg dose is also significantly better than placebo between 1 and 4 hours for both endpoints. In adolescents, ZNS 5 mg is superior to placebo on the 2-hour pain-free rate with a clinically significant effect size larger than 11% (30% vs. 17%) as well as the 2-hour

headache response (51% vs. 39%). ZNS 2.5 mg is superior on the 2-hour headache response (53% vs. 39%). ZNS was also effective in reducing associated migraine symptoms for patients who had these symptoms at baseline and in reducing the proportion of patients requiring a rescue medication from 2 to 24 hours post treatment. In adults, the most common adverse reactions (ARs) (≥ 5% and > placebo) in clinical trials were unusual taste, paresthesia, hyperesthesia, and dizziness. The incidence of ARs was generally dose related. In adolescents, the most common AR was dysgeusia (10% vs. 6% vs. 2% for ZNS 5 mg vs. 2.5 mg vs. placebo). Other common ARs were nasal discomfort, dizziness, oropharyngeal pain, and nausea. ZNS 2.5 mg is the recommended starting dose for adults and adolescents.

The current protocol is designed to apply many of the relevant learnings from previous pediatric acute migraine trials to elementary school-age children who are suffering with this disorder.

Study IPX229-B16-01 will employ the following methodology:

- Crossover design to leverage within-subject variability, which is expected to be lower than between subjects.
- Enrichment strategy: Similar to the ZNS adolescent TEENZ Study (D1220C00001), the use of a placebo-challenge run-in period whereby subjects treat a separate attack to identify and exclude placebo-responders prior to randomization without inserting timely treatment delays.
- Similar to the TEENZ Study, use of migraine duration criteria (≥ 3 hours) to facilitate the ability to differentiate active drug from placebo because of the shorter duration of some pediatric migraine attacks.
- Use of revised ICHD-II diagnostic criteria for migraine (ICHD-3B) to increase diagnostic sensitivity for pediatrics.
- Primary efficacy endpoint is the proportion of subjects who achieve pain-free status at 2 hours based on data from subjects treated with the high dose from each stratum.
- Use of weight-based dosing.

5. TRIAL OBJECTIVES AND PURPOSE

To evaluate the efficacy and safety of ZNS in the acute treatment of migraine headache in subjects ages 6 to 11 years.

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

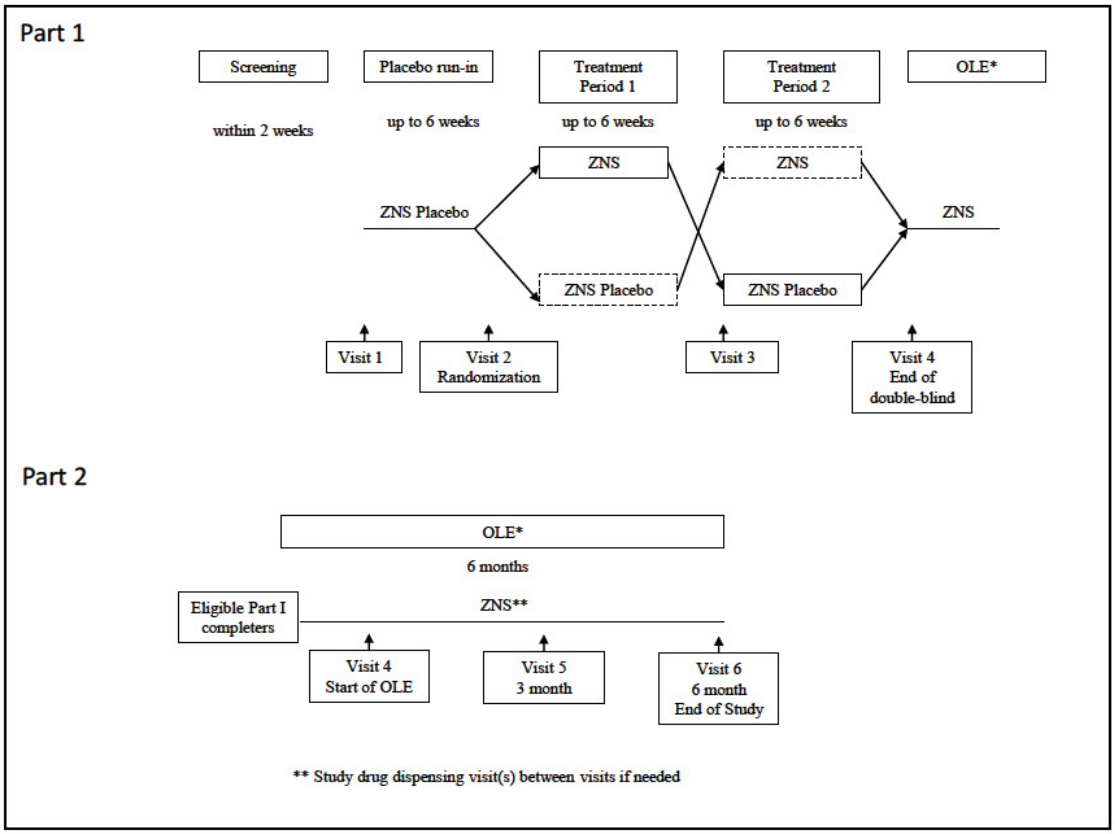
This is a randomized, double-blind, placebo-controlled, 2-period, crossover outpatient study (See Figure 1). Within 2 weeks of screening, eligible subjects will return to the study site to begin a 6-week single-blind run-in period, during which a single migraine headache will be treated with 1 dose of placebo. Subjects will be instructed to treat a headache of moderate or severe pain intensity within approximately 20 minutes of onset of headache pain reaching moderate or severe intensity and to complete a diary capturing the headache severity using a 4-point headache pain intensity scale (severe = 3, moderate = 2, mild = 1 or no pain = 0), other associated symptoms (Appendix B) and use of rescue medication(s). Headaches occurring while the child is at school will not be treated with study drug. Adverse events (AEs) will also be collected. Diary entries are to be recorded prior to treatment with study drug and after treatment at 30 minutes and at 1 and 2 hours. If, after 2 hours, the migraine headache has not responded (ie, reduced to a pain intensity of mild or no pain), the subject is permitted to use protocol-allowed rescue medication(s). Any subsequent migraine episodes during the run-in period will be treated with the subject's protocol-allowed pre-study acute migraine medication. Subjects who have not treated a migraine headache with blinded placebo during the 6-week run-in period will be considered screen failures. Placebo challenge responders (defined as those subjects who treat a migraine attack of moderate (2) or severe (3) intensity and who achieve a mild (1) or no pain (0) response within 2 hours after dosing) will be discontinued from the study.

Eligible placebo non-responders will be randomized to one of two treatment sequences within their respective body weight stratum determined immediately prior to randomization: ZNS followed by placebo or placebo followed by ZNS (Table 2). Subjects weighing less than 50 kg will be allocated randomly to receive ZNS 2.5 mg or 1 mg in a 5:1 fashion during the ZNS treatment. Subjects weighing at least 50 kg will be allocated randomly to receive ZNS 5 mg or 2.5 mg in a 5:1 fashion during the ZNS treatment (Table 3). Following randomization, subjects will have up to 6 weeks to treat a migraine attack of moderate or severe intensity. During each treatment period, subjects will treat a moderate to severe migraine attack within approximately 20 minutes of the headache pain reaching moderate or severe intensity. Headaches occurring while the child is at school will not be treated with study drug. Headache pain intensity is assessed by the subjects at 30 minutes and at 1, 2, and 24 hours post-dose using a subject diary containing the 4-point headache pain intensity scale. Subjects who do not obtain satisfactory relief of migraine pain by 2 hours after taking study drug are permitted to treat with their protocol-allowed pre-study acute migraine medication (eg, nonsteroidal anti-inflammatory drugs [NSAIDs] or acetaminophen) at that time or at any time thereafter, if the headache does not resolve or if it recurs, with the exception that all triptans and ergot derivatives are prohibited for 24 hours following the last dose of study treatment. After treating a migraine attack in the first treatment period, the subject will return to the study site to receive study drug for the second treatment period. Subjects will then have up to 6 weeks to treat a second migraine attack of moderate or severe intensity.

Subjects who successfully complete the double-blind portion of this study and continue to be eligible will be offered participation in a 6-month outpatient open-label safety extension (OLE)

where they will treat up to 4 migraine attacks per month with ZNS. Headaches occurring while the child is at school will not be treated with study drug. During the OLE, subjects will assess their pain-free status at 2 hours for each migraine attack treated with ZNS. Migraine-associated disability, using the PedMIDAS questionnaire, will be assessed at the end of study.

Figure 1: Study Flow Chart



6.2. Number of Subjects

Approximately 393 subjects will be enrolled to randomize 264 so that at least 180 subjects will complete both double-blind treatment periods. With the 5:1 (high dose:low dose) randomization ratio for the two weight strata, it is estimated that 150 high-dose subjects will complete both double-blind treatment periods and 30 subjects randomized to the lower dose level will complete both double-blind treatment periods. Approximately 100 subjects who complete the double-blind crossover phase will enter the 6-month open-label safety extension (OLE) to enable at least 50 subjects to complete at least 6 months treating on average at least one migraine attack per month (treating up to 4 migraine attacks per month) with ZNS.

6.3. Treatment Assignment

Table 2: Randomization Schedule for Study IPX229-B16-01

	Treatment Period 1	Treatment Period 2
Sequence 1	ZNS	ZNS Placebo
Sequence 2	ZNS Placebo	ZNS

Subjects weighing less than 50 kg will be allocated randomly to receive ZNS 2.5 mg or 1 mg in a 5:1 fashion during the ZNS treatment. Subjects weighing at least 50 kg will be allocated randomly to receive ZNS 5 mg or 2.5 mg in a 5:1 fashion during the ZNS treatment. The two dose levels are described in Table 3.

Table 3: Dose Levels during Double-Blind Treatment Period

Weight (kg)	Dose Level (Number Randomized)	
	Low (n=44)	High (n=220)
<50	1 mg	2.5 mg
≥50	2.5 mg	5 mg

During the OLE, all eligible subjects will receive ZNS.

6.4. Dose Adjustment Criteria

Following randomization, no dose adjustments are allowed during the double blind portion of the study. Subjects who cannot tolerate the assigned dose will be discontinued from the study.

During the OLE, all subjects weighing less than 50 kg will receive ZNS 2.5 mg and those 50 kg or more will receive ZNS 5 mg. The 1 mg dose strength will not be available for the OLE portion of this study. Subjects weighing less than 50 kg who are unable to tolerate the 2.5 mg dose will be discontinued. Subjects who are receiving 5 mg may reduce the dose from 5 mg to 2.5 mg if needed; however, subjects who are receiving 2.5 mg cannot escalate to 5 mg unless they weigh at least 50 kg.

6.4.1. Rationale for Dose Selection

Doses of 2.5 and 5 mg were chosen for the higher weight cohort and doses of 2.5 and 1 mg were selected for the lower weight cohort since the AUC and C_{max} for these doses are expected to be comparable to those noted in adults and adolescents at doses of 5 and 2.5 mg, which have been shown to be efficacious in previous studies.

6.5. Criteria for Study Termination

The Sponsor has the right to terminate this study and remove all study material from the study site at any time for medical or administrative reasons. The Sponsor will endeavor to give adequate notice to allow safe withdrawal of subjects from the study.

6.6. Restrictions During the Study

The following restrictions apply in this study during the single-blind run-in and during the double-blind treatment period:

1. Subjects must treat headache with the study drug within approximately 20 minutes of headache pain reaching moderate or severe intensity.
2. Subjects must be completely symptom-free from any previous headache prior to treating a migraine headache with study drug.
3. Subjects must initiate treatment of the moderate or severe migraine headache with only the study drug provided, unless the headache occurs while the child is attending school. The nasal spray device is for single use and will contain only 1 dose of study drug. If the migraine does not improve to mild or no pain within 2 hours post dose, the subject has the option to use rescue medication(s). A 2nd dose of study drug will not be allowed as rescue medication, nor will it be provided. Rescue medication(s), as allowed by the protocol and the investigator, may be taken 2 hours after taking the study drug and may include NSAIDS, anti-emetics, analgesics (eg, opioids), or sedatives. Rescue medication(s) will not be provided by the sponsor.
4. Before taking the study drug, subjects must not have:
   - Treated this headache with any other medication,
   - Received any ergotamine or ergotamine-like derivative (eg, dihydroergotamine, methysergide) or triptan ($5HT_{1B/1D}$ agonist) in the 24-hour period before treatment with the study drug,
   - Used opiates in the last 24 hours.
5. After taking the study drug, subjects will be instructed not to:
   - Sleep or nap for at least 2 hours post dose,
   - Use rescue medication(s) within 2 hours of taking the study drug (see above for use of rescue medication),
   - Use an ergotamine or ergotamine-like derivative (eg, dihydroergotamine, methysergide) or non-study triptans ($5HT_{1B/1D}$ agonist) for 24 hours.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Part 1

7.1.1. Subject Inclusion Criteria

1. Each child must have a responsible trained adult with knowledge of the conduct of the study and must be available to supervise migraine treatment and study requirements. Parent or legal guardian is able to provide written informed consent and subject is able to provide written assent.
2. Subjects ages 6 to 11 years at the time of screening; subjects must not be enrolled if they will turn 12 years of age within 14 weeks after randomization (Visit 2).
3. An established diagnosis of migraine (history indicating the presence of migraine for at least 6 months) with or without aura as defined by the ICHD-3B revised criteria (See Appendix A).
4. By history, average migraine frequency of ≥ 2 attacks per month of moderate or severe intensity lasting on average ≥ 3 hours per attack untreated and not experiencing satisfactory relief with NSAIDs or acetaminophen.
5. By history, migraine attacks occur at intervals of > 24 hours apart.
6. By history, experiences at least 16 headache-free days per month on average for 3 months before Screening.
7. Has the ability to differentiate between migraine and non-migraine headaches.
8. Postmenarche females agree to use a medically acceptable method of contraception throughout the study and for 1 month after completing the study.
9. Postmenarche females have a negative urine pregnancy test at Screening.
10. Clearly understands and is likely to comply with all study procedures, including completion of the subject diary and scheduled visits, as demonstrated during the single-blind run-in period.

7.1.2. Subject Exclusion Criteria

1. History of ischemic or vasospastic heart disease, arrhythmias associated with accessory conduction pathways (eg, Wolff-Parkinson-White syndrome), cerebrovascular disease, hemiplegic or basilar artery migraine, peripheral vascular disease, ischemic bowel disease, uncontrolled hypertension, recent (within 24 hours) or use of another 5HT1 agonist, ergots or ergotamine-containing medications.
2. Any medical condition, including severe hepatic impairment, which, in the opinion of the investigator, may put the subject at increased risk with exposure to zolmitriptan, or may interfere with the safety or efficacy assessments.
3. Use of monoamine oxidase-A (MAO-A) inhibitor, methysergide, methylergonovine, or cimetidine in the 3 weeks before Screening or the new use or dose of an selective

serotonin reuptake inhibitors (SSRI) or serotonin–norepinephrine reuptake inhibitors (SNRI) within 4 weeks before Screening.

4. Clinically significant abnormalities indicated from the medical history, physical examination, 12-lead electrocardiogram (ECG), and clinical laboratory assessments (chemistry, hematology, and urinalysis).
5. For a subject who is 9 years of age or older at Screening, has a positive urine drug screen not explained by the use of appropriately prescribed rescue or other physician-prescribed medications.
6. Had an unacceptable adverse experience following previous use of any $5HT_{1B/1D}$ agonist drug (in the opinion of the investigator).
7. Had not experienced satisfactory relief from migraine pain during prior treatment with 2 or more adequate courses of triptans.
8. Has a diagnosis or suspicion of drug-induced or chronic daily headaches within past year.
9. Prior use of any nasal spray (triptan or dihydroergotamine [DHE]) for the acute treatment of migraine.
10. Has any recent history of abuse (in the previous year) of alcohol or other drugs including drugs for the acute treatment of headache.
11. Disease or anatomic abnormalities of the nasal cavity precluding or complicating the use of ZNS.
12. Family member of the investigator, study site personnel or sponsors.
13. Is currently participating or has participated in another clinical study within 30 days prior to screening for this study.

7.2. Part 2

7.2.1. Subject Inclusion Criteria

1. Has successfully completed Part 1.
2. All postmenarche females agree to use a medically acceptable method of contraception throughout Part 2 and for 1 month after completing the study.

7.2.2. Subject Exclusion Criteria

1. In the opinion of the investigator, the subject should not participate in the study.
2. For a subject who is 9 years of age or older, has a positive urine drug screen not explained by the use of appropriately prescribed rescue or other physician-prescribed medications.
3. Disease or anatomic abnormalities of the nasal cavity precluding or complicating the use of ZNS.
4. Family member of the investigator, study site personnel or sponsors.

5. Is planning to participate in another clinical study during Part 2.

7.3. Subject Withdrawal Criteria

Site personnel should make every effort to conduct all protocol-specific procedures to complete the study. A subject may be discontinued from the study due to the following reasons:

1. Withdrawal by subject
2. Adverse event (AE)
3. Lack of efficacy
4. Study terminated by Sponsor
5. Protocol deviation
6. Noncompliance with study drug
7. Lost to follow-up
8. Death
9. Other

8. STUDY PROCEDURES

The procedures to be performed at each study visit are described below and summarized in Table 4.

Table 4: Study Design and Schedule of Assessments

	Screening	Single-Blind Run-in	Treatment Period 1	Treatment Period 2	End of DB/ Start of OLE	Study Drug Resupply if Needed	3 Months OLE	Study Drug Resupply if Needed	6 Months/ End of OLE
Visits	**Visit 0**	**Visit 1**	**Visit 2 Random-ization[a]**	**Visit 3**	**Visit 4**	**Month 0-3**	**Visit 5**	**Month 4-6**	**Visit 6 (EOS)**
Study Week	**-2**	**0**	**6**	**12**	**18**				
Assessment									
Informed Consent, Assent and HIPAA authorization	X								
Contact IWRS	X	X	X	X	X	X	X	X	X
Inclusion/ Exclusion	X	X			X[e]				
Medical History	X								
Height/Weight	X		X		X		X		X
Physical examination	X				X				X
12-lead ECG	X				X				X
Vital Signs	X	X	X	X	X		X		X
Clinical Laboratory tests[b]	X				X				X
Urine Pregnancy test[c]	X								
Drug Screen[d]	X								
Adverse Events	X	X	X	X	X		X		X
Concomitant Medications	X	X	X	X	X		X		X
Training on use of nasal spray device		X	as needed	as needed					
Dispense study drug		X	X	X	X[e]	X	X	X	

	Screening	Single-Blind Run-in	Treatment Period 1	Treatment Period 2	End of DB/ Start of OLE	Study Drug Resupply if Needed	3 Months OLE	Study Drug Resupply if Needed	6 Months/ End of OLE
Visits	**Visit 0**	**Visit 1**	**Visit 2 Random-ization[a]**	**Visit 3**	**Visit 4**	**Month 0-3**	**Visit 5**	**Month 4-6**	**Visit 6 (EOS)**
Study Week	**-2**	**0**	**6**	**12**	**18**				
Diary Training		X	X[f]	X[f]	X[f]		X[f]		
Dispense Diary		X	X	X	X[e]		X		
Collect and Review Diary			X	X	X		X		X
PedMIDAS[g]			X						X
Reminder phone call[h]			X	X	X		X		X
C-SSRS[i]	X	X	X	X	X		X		X
Collect study drug/perform accountability			X	X	X		X		X

Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale, DB = double blind, ECG = electrocardiogram, EOS = End of Study, HIPAA = Health Insurance Portability and Accountability Act, IWRS = Interactive Web and Voice Response System, PedMIDAS = Pediatric Migraine Disability Assessment, PK = pharmacokinetic(s), OLE = open-label safety extension.

[a] If subject discontinues at Visit 2, perform the following procedures: collect study drug and subject diary; update the concomitant medications and AE pages; measure vital signs (blood pressure, heart rate, respiratory rate, and oral temperature); administer the C-SSRS Children's Since Last Visit (Appendix D), and contact IWRS to report discontinuation from study.

[b] See Appendix E.

[c] Postmenarche females.

[d] Subjects ages 9 and older.

[e] Only applicable to subjects entering OLE.

[f] Diary retraining, as necessary.

[g] See Appendix C.

[h] Reminder phone calls on the days before Visit 2-6 to remind subject to return used devices and unused study drug and to bring their subject diary(ies).

[i] See Appendix D.

8.1. Screening Visit

Parents or legal guardians must provide written informed consent to participate in the study prior to any study specific procedures. Subjects must give assent in order to participate in the study. After obtaining the signed Informed Consent Form (ICF), Informed Assent Form (IAF) and Health Insurance Portability and Accountability Act (HIPAA) authorization, complete the following procedures and assessments:

- Assign a 6-digit ID number to each subject using the Interactive Web Response System (IWRS).
- Determine eligibility to participate in the study based on the inclusion and exclusion entry criteria
- Measure vital signs (blood pressure, heart rate, respiratory rate, and oral temperature)
- Perform urine pregnancy test on postmenarche females
- Perform urine screen for drugs of abuse (subjects ages 9 and older)
- Take a complete medical history
- Perform a physical exam including height and weight
- Perform a 12-lead ECG
- Collect blood and urine samples for clinical laboratory studies
- Record concomitant medications including medications taken for migraines within 30 days prior to screening
- Perform the Columbia–Suicide Severity Rating Scale (C-SSRS) Baseline/Screening Children's scale (Appendix D).

Notify individuals who successfully complete screening procedures following review of all study entry criteria and clinical laboratory results of eligibility outcome.

The interval between Screening and Visit 1 should not exceed 2 weeks.

8.2. Visit 1 – Part 1 Single-Blind Run-In

8.2.1. Before Visit 1

- Schedule eligible subjects to return to the study site within approximately 2 weeks of screening

8.2.2. Visit 1

- Ensure that the subject continues to meet the inclusion/exclusion criteria for the study.
- Measure vital signs (blood pressure, heart rate, respiratory rate, and oral temperature)
- Update any concomitant medication changes

- Record any adverse events
- Perform the C-SSRS Children's Since Last Visit (Appendix D)
- Review with the subjects and the caregivers that study drug should be used for migraine headaches only.
- Train the subjects and the caregivers on the gradations of migraine headache severity
- Dispense Diary
- Train the subjects and the caregivers on how to complete the diary capturing the subject's headache severity by using the 4-point headache pain intensity scale at various time points.
  - Diary entries should be recorded prior to treatment with the study drug and at 30 minutes and at 1, 2, and 24 hours after treatment.
- Train the subjects and the caregivers on how to use the nasal spray. The nasal spray training device will not be dispensed to the subject and will be retained at the clinical site.
- Assign study drug using IWRS
  - Dispense study drug
- Remind subjects and the caregivers of the following regarding use of the study drug:
  1. Before using the study drug device, they must not have:
     - Treated the headache with any other medications
     - Received any ergotamine or ergotamine like derivates (eg, dihydroergotamine, methysergide) or triptans ($5HT_{1B/1D}$ agonist) in the 24-hour period prior to treatment with the study drug
     - Used opiates in the last 24 hours
  2. They should treat a migraine headache within approximately 20 minutes of onset of it reaching moderate or severe intensity. Headaches occurring while the child is at school will not be treated with study drug.
  3. If after 2 hours, the migraine headache has not responded (ie, reduced to a pain intensity of mild or none), they may use their protocol-allowed pre-study acute migraine medication(s)
- Any subsequent migraine episodes will be treated with the subject's protocol-allowed pre-study acute migraine medication(s).

8.3. Visit 2 (Randomization, First Treatment) and Visit 3 (Second Treatment) – Part 1

8.3.1. Before Visit 2 and 3

- Call the subject/caregiver and remind him/her of the following:

- Return used devices and unused study drug
- Bring subject diary

8.3.2. Visit 2 and 3

At Visit 2, subjects will be discontinued from the study for any of the following reasons:

- Subjects who have not treated a migraine headache with study drug during the 6-week run-in period.
- Placebo challenge responders (defined as those subjects who treat a moderate or severe migraine headache and who achieve mild or no pain at any time point within 2 hours after dosing).

If the subject is discontinued at Visit 2, perform the following procedures:

- Collect study drug and subject diary
- Update the concomitant medications and AE pages
- Measure vital signs (blood pressure, heart rate, respiratory rate, and oral temperature)
- Perform the C-SSRS Children's Since Last Visit (Appendix D)
- Contact IWRS to report discontinuation from study.

At Visit 2 and 3:

- Collect the previously dispensed study drug and perform accountability
- Collect and review subject diary
- Retrain on diary completion as necessary. Review with the subjects and the caregivers how to complete the diary capturing the subject's headache severity by using the 4-point headache pain intensity scale at various time points
- Measure vital signs (blood pressure, heart rate, respiratory rate, and oral temperature)
- Measure height and weight (Visit 2 only)
- At Visit 2 only, have the subjects complete PedMIDAS (Appendix C)
- Perform the C-SSRS Children's Since Last Visit (Appendix D).
- Record and update any AEs and concomitant medications since last visit
- Review with the subjects and the caregivers that study drug should only be used for the treatment of migraine headaches.
- Review with the subjects and the caregivers the gradations of migraine headache severity and the importance of only using the study drug to treat migraine headaches that reach moderate to severe intensity
- Review dosing instructions using the training nasal spray device as needed
- Remind subjects and the caregivers of the following regarding use of the drug:

  - Before using the study drug device, they must not have:
    - Treated the headache with any other medications
    - Received any ergotamine or ergotamine like derivates (eg, dihydroergotamine, methysergide) or triptan ($5HT_{1B/1D}$ agonist) in the 24-hour period prior to treatment with the study drug
    - Used opiates in the last 24 hours

- At Visit 2, randomize eligible subjects using the IWRS to one of two treatment sequences: ZNS followed by placebo, or placebo followed by ZNS.
- At Visit 3, dispense study drug using IWRS
- During treatment with ZNS subjects weighing less than 50 kg will receive ZNS 1 mg or ZNS 2.5 mg and those weighing 50 kg or more will receive ZNS 2.5 mg or ZNS 5 mg.
- Dispense the subject diary.
- During each treatment period, subjects will treat a moderate or severe migraine attack within approximately 20 minutes of the headache pain reaching moderate or severe intensity. Headaches occurring while the child is at school will not be treated with study drug.
- Subjects will have up to 6 weeks to experience and treat a migraine attack of moderate or severe intensity
- Headache pain severity will be assessed by the subjects at 30 minutes and at 1, 2 and 24 hours post dose using the subject diary containing the 4-point headache pain intensity scale.
- Subjects who do not obtain satisfactory relief of migraine pain by 2 hours after taking study drug are permitted to treat with their usual protocol-allowed pre-study acute migraine medication (eg, NSAIDs or acetaminophen) at that time or at any time thereafter if the headache does not resolve or if it recurs, with the exception that all triptans and ergot derivates are prohibited for 24 hours following the last dose of study drug.

8.4. Visit 4 End of Double Blind and Start of OLE – Part 2

8.4.1. Before the End of Double Blind and Start of OLE (Visit 4)

- Call the subject/caregiver to remind him/her of the following:
  - Return used devices and unused study drug
  - Bring subject diaries

8.4.2. End of Double Blind and Start of OLE (Visit 4)

End of Double Blind (Part 1):

- Collect previously dispensed study drug
- Collect and review subject diaries
- Retrain on diary completion as necessary
- Measure vital signs (blood pressure, heart rate, respiratory rate, and oral temperature)
- Complete physical examination including height and weight
- Perform 12-lead ECG
- Obtain blood and urine samples for clinical laboratory evaluations (chemistry, hematology and urinalysis)
- Record any AEs and update any changes to concomitant medications since last visit
- Perform the C-SSRS Children's Since Last Visit (Appendix D).

Start of OLE (Part 2):

Subjects who complete the double-blind portion of the study and meet the eligibility criteria may participate in a 6-month open-label safety extension (OLE) where they may treat up to 4 migraine attacks of moderate or severe intensity per month with study drug.

- Determine eligibility to participate in the OLE based on the inclusion and exclusion entry criteria.
- During the OLE, subjects weighing less than 50 kg will receive ZNS 2.5 mg and those weighing 50 kg or more will receive ZNS 5 mg. The 1 mg spray will not be available for the open-label extension (OLE). Subjects weighing less than 50 kg who are unable to tolerate the 2.5 mg dose will be discontinued. Subjects who are receiving 5 mg may reduce the dose to 2.5 mg if needed; however, no subjects can escalate to 5 mg unless they weigh at least 50 kg.
- Contact IWRS and dispense study drug.
- Headaches occurring while the child is at school will not be treated with study drug.
- Remind subjects and the caregivers of the following regarding use of the study drug:
  - Before using the study drug device, they must not have:
    - Treated the headache with any other medications
    - Received any ergotamine or ergotamine like derivates (eg, dihydroergotamine, methysergide) or triptan ($5HT_{1B/1D}$ agonist) in the 24-hour period prior to treatment with the study drug
    - Used opiates in the last 24 hours
- Instruct subjects to only treat headaches that reach moderate or severe pain intensity and to treat each of these headaches within approximately 20 minutes of onset of

headache pain reaching moderate or severe intensity. For each treated headache, subjects complete a diary capturing the headache severity using a 4-point headache pain intensity scale (severe = 3, moderate = 2, mild = 1 or no pain = 0).

- Instruct subjects of the following: If satisfactory relief of the migraine pain is not achieved by 2 hours after taking study drug, they are permitted to treat the migraine with another dose of study drug, with approved rescue medications, or a combination of both, provided it is at least 2 hours after the first dose of study drug. No more than 2 doses of study drug within 24 hours are allowed.
- Dispense subject diaries and instruct subjects to complete the headache pain severity at predose and at 2 hours postdose using the 4-point headache pain intensity scale.
- Subject should return within 3 months for Visit 5.
- If needed, subject may return to the site for study drug resupply.

8.5. Visit 5 – OLE 3 months

8.5.1. Before Visit 5

- Call the subject/caregiver and remind him/her of the following:
  - Return used devices and unused study drug
  - Bring subject diaries

8.5.2. Visit 5

- Collect the previously dispensed study drug and perform accountability
- Collect and review subject diaries
- Retrain on diary completion as necessary
- Measure vital signs (blood pressure, heart rate, respiratory rate, and oral temperature)
- Measure height and weight
- Perform the C-SSRS Children's Since Last Visit (Appendix D).
- Record and update any AEs and concomitant medications since last visit
- Subjects weighing less than 50 kg will receive ZNS 2.5 mg and those weighing 50 kg or more will receive ZNS 5 mg. The 1 mg spray will not be available for the open-label extension (OLE). Subjects weighing less than 50 kg who are unable to tolerate the 2.5 mg dose will be discontinued. Subjects who are receiving 5 mg may reduce the dose to 2.5 mg if needed; however, no subjects can escalate to 5 mg unless they weigh at least 50 kg.
- Contact IWRS and dispense the study drug.
- Headaches occurring while the child is at school will not be treated with study drug.
- Remind subjects and the caregivers of the following regarding use of the study drug:

  - Before using the study drug device, they must not have:
    - Treated the headache with any other medications
    - Received any ergotamine or ergotamine like derivates (eg, dihydroergotamine, methysergide) or triptan ($5HT_{1B/1D}$ agonist) in the 24-hour period prior to treatment with the study drug
    - Used opiates in the last 24 hours.
- Instruct subjects to only treat headaches that reach moderate or severe pain intensity and to treat each of these headaches within approximately 20 minutes of onset of headache pain reaching moderate or severe intensity. For each treated headache, subjects complete a diary capturing the headache severity using a 4-point headache pain intensity scale (severe = 3, moderate = 2, mild = 1 or no pain = 0).
- Subjects who do not obtain satisfactory relief of the migraine pain by 2 hours after taking study drug are permitted to treat with another dose of study drug, or with protocol-allowed pre-study acute migraine medication, or with a combination of both, provided it is at least 2 hours after the first dose of study drug. No more than 2 doses of study drug within 24 hours should be administered.
- Dispense subject diaries
- Headache pain severity will be assessed by the subjects immediately predose and at 2 hours postdose using the subject diary containing the 4-point headache pain intensity scale.
- Subject should return within 3 months for Visit 6
- If needed, subject may return to the site between visits for study drug resupply.

8.6. Visit 6 — OLE 6 months (End of OLE)

8.6.1. Before Visit 6

- Call the subject/caregiver to remind him/her of the following:
  - Return used devices and unused study drug
  - Bring subject diary

8.6.2. Visit 6

- Collect study drug and perform accountability
- Collect and review subject diaries
- Measure vital signs (blood pressure, heart rate, respiratory rate, and oral temperature)
- Complete physical examination including height and weight
- Perform 12-lead ECG

- Obtain blood and urine samples for clinical laboratory evaluations (chemistry, hematology and urinalysis)
- Perform the C-SSRS Children's Since Last Visit (Appendix D)
- Record and update any AEs and concomitant medications since last visit
- Have the subjects complete PedMIDAS (Appendix C)
- Contact IWRS to report completion of the study

8.7. Early Discontinuations Post-Randomization During Double-Blind Period or OLE

Perform the following procedures on subjects who discontinue post-randomization:

- Collect and review subject diaries
- Measure vital signs (blood pressure, heart rate, respiratory rate, and oral temperature)
- Complete physical examination including height and weight
- Perform 12-lead ECG
- Obtain blood and urine samples for clinical laboratory evaluations (chemistry, hematology and urinalysis)
- Record any AEs and update any changes to concomitant medications since last visit
- Perform the C-SSRS Children's Since Last Visit (Appendix D).
- Contact IWRS to report discontinuation from study

9. TREATMENT OF SUBJECTS

9.1. Description of Study Drug

Study drugs will be provided by Impax for this study: ZNS in three zolmitriptan strengths, 1 mg, 2.5 mg and 5 mg, and ZNS placebo (Table 5). The ZNS will contain 1 dose of study drug, and the placebo ZNS will contain 1 dose of placebo.

Subjects weighing less than 50 kg will be randomized 5:1 to receive ZNS 2.5 mg or ZNS 1 mg and those weighing 50 kg or more will be randomized 5:1 to receive ZNS 5 mg or ZNS 2.5 mg.

Table 5: Study Drugs for Study IPX229-B16-01

Investigational Product	Dosage form and strength	Manufacturer
Zolmitriptan Nasal Spray 10 mg/mL	1 mg nasal spray	AstraZeneca
Zolmitriptan Nasal Spray 25 mg/mL	2.5 mg nasal spray	AstraZeneca
Zolmitriptan Nasal Spray 50 mg/mL	5 mg nasal spray	AstraZeneca
Placebo for Zolmitriptan Nasal Spray	ZNS placebo	AstraZeneca

9.2. Permitted Concomitant Medications

Subjects will be allowed to continue any of their regular medications being taken at the time of entry into the study (other than acute abortive migraine or restricted medications noted in Section 9.3. These allowed medications include non-migraine medications and medications taken for migraine prophylaxis, as long as the dose and dosing regimen has been stable for at least 4 weeks prior to screening and is intended to remain stable throughout the double-blind portion of this study, and provided it is for a condition that is stable, and in the investigator's opinion, not adversely affected by participation in the study.

If the subject has been on stable dose and regimen of an SSRI or SNRI for 8 weeks prior to Screening and intends to continue on this dose/regimen throughout this study, they may be included in the study.

9.3. Prohibited Medications

Use of a monoamine oxidase-A (MAO-A) inhibitor, methysergide, methylergonovine, or cimetidine in the 3 weeks before Screening or the new use or dose of an SSRI or SNRI within

4 weeks before Screening; recent (within 24 hours of study drug administration) use of another 5HT-1 agonist (eg, another triptan) or an ergot-type medication is prohibited.

9.4. Treatment Compliance

Study drugs will be dispensed at the study sites. Study drug accountability and reconciliation will be performed by the study staffs and by the study monitor.

9.5. Randomization and Blinding

At Visit 2, the subject will be randomized into 1 of 2 treatment sequences (See Section 6.3 Treatment Assignment). The randomization will be stratified by weight and for high and low dose group in 5:1 ratio.

This is a double-blind, randomized, placebo-controlled study with efficacy assessments done in the outpatient setting by elementary school-age children (with the assistance of a trained adult) all of whom are blinded to treatment assignments.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

Study drugs include ZNS in three zolmitriptan strengths, 1 mg, 2.5 mg and 5 mg, and placebo for ZNS. ZNS or placebo will be provided by the Sponsor or designee.

10.2. Study Drug Packaging and Labeling

Sponsor or designee will provide study drugs to the study sites. Labels will be prepared in accordance with GMP and local regulatory guidelines.

10.3. Study Drug Storage

All study drug should be kept in secure place under appropriate storage conditions specified on the investigational product label.

10.4. Study Drug Administration

The administration of all medication (including study drug) should be recorded in the appropriate sections of the eCRF.

10.5. Study Drug Dispensing and Accountability

The Investigator must ensure that all study medication received at the study site is inventoried and accounted for, and that dispensed study medication is recorded in the subject's source documents, the CRF, and the study medication inventory log. Site personnel must not relabel or reassign study medication to other subjects or to individuals not enrolled in the study. The study monitor verifies medication accountability during monitoring visits.

10.6. Study Drug Handling and Disposal

The Investigator must retain and properly store all partially used and unused study drug until authorized by Impax regarding disposition.

11. ASSESSMENT OF EFFICACY

- Primary: Proportion of subjects who achieve pain-free status at 2 hours based on data from subjects treated with the high dose from each stratum (2.5 mg in the low weight stratum and 5 mg in the high weight stratum). "Pain-free" is defined as a reduction in moderate (2) or severe (3) pain to no (0) pain.
- Secondary: All endpoints will be summarized by the proportion of subjects (except time to use of rescue medications) treated with the high and low dose levels (Table 3).
  - Pain-free status at 2 hours post-dose for the low dose level.
  - Pain-free status at the following additional time points: 30 minutes and at 1 and 24 hours post-dose.
  - Absence of associated migraine symptoms (photophobia, phonophobia, nausea) at the following time points: 30 minutes and at 1, 2, and 24 hours post-dose.
  - Headache response. A "headache response" is defined as a reduction in moderate (2) or severe (3) pain to mild (1) or no (0) pain. Headache response at the following time points: 30 minutes and at 1, 2, and 24 hours post-dose.
  - Incidence and time to use of rescue medication up to 24 hours post-dose.
  - Headache recurrence rates 2 to 24 hours post treatment for the subset of subjects who attained a 2-hour pain-free and/or a 2-hour headache response and who don't use any rescue medication.
  - Sustained headache response and sustained pain free response 2 to 24 hours post-dose
- Clinical Utility Assessments During the OLE:
  - Proportion of subjects who report pain-free status at 2 hours for each migraine attack that reaches moderate or severe intensity and is treated with the study drug.
  - PedMIDAS (Hershey et al 2001) to measure the impact of migraine-associated disability at randomization and at end of OLE (3 domains: school, home, and social activities)

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

Safety will be assessed by the following parameters: Adverse events, clinical laboratory tests, 12-lead ECGs, vital signs, and physical examinations.

12.2. Adverse Events

12.2.1. Definition of Adverse Events

An adverse event (adverse experience) is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

All AEs and any clinically significant physical examination findings, 12-lead ECG abnormalities, or clinical laboratory measurements occurring during the study that were not present prior to administration of study medication and that continue at Study Exit should be followed and evaluated with additional tests, if necessary, until the AEs are medically stable or resolved. Follow-up on these AEs should be recorded on the source documents and reported to Impax.

12.2.2. Recording Adverse Events

Elicit information about AEs with nonselective questions such as: "Have you experienced any changes in your health status since your last visit?" Encourage subjects to report AEs at onset.

Record information for any AE that emerges from the time the subject signs the ICF until Study Exit.

Monitor each subject closely for the development of AEs and record all such events on the AE page of the CRF. Whenever possible, group signs and symptoms that constitute a single diagnosis. For example, cough, rhinitis, and sneezing might be grouped as upper respiratory infection.

For each AE, record the onset date, severity, seriousness, relationship to study medication, date of resolution (or continuing), action taken, and outcome in the CRF. The Investigator is to make a causality assessment (relationship to study medication) for every AE.

12.2.3. Follow-up

The Investigator must follow each AE until resolved or medically stable.

12.2.4. Relationship to Study Drug

The Investigator documents his/her opinion of the relationship of the AE to the study medication as follows:

- Not Related—the experience can be readily explained by the subject's underlying medical condition or concomitant medications and no relationship exists between the study medication and the experience.
- Unlikely Related—the temporal relationship between the AE and the administration of the study medication is uncertain and it is likely that the AE can be explained by the subject's medical condition or other therapies.
- Possibly Related—there is some logical temporal relationship between the AE and the administration of the study medication and the experience is unlikely to be explained by the subject's medical condition or other therapies.
- Related—the temporal relationship is compelling between the administration of the study medication and the AE cannot be explained by the subject's medical condition or other therapies.

12.2.5. Assessment of Severity

Grade each AE for severity and note in the description of the AE. Determine the severity category of mild, moderate, or severe, as defined below, and enter the information on the AE page of the CRF.

- Mild—causing no limitation of usual activities
- Moderate—causing some limitation of usual activities
- Severe—causing inability to carry out usual activities

12.3. Serious Adverse Event (SAE)

12.3.1. Definition of Serious Adverse Event

A serious adverse event (SAE) is any AE occurring at any dose that results in any of the following outcomes, regardless of relationship to the study medication:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

12.3.2. Reporting Serious Adverse Events

Any SAE that occurs from the time the subject signs an ICF until 30 days after taking the final dose of study medication must be reported by the investigative staff to the Sponsor or the

Sponsor's representative within 24 hours of knowledge of the event (see Study Contact Information).

An SAE form must be completed and sent to the Sponsor and/or the Sponsor's representative. All SAEs must also be recorded on the AE page of the CRF. Additionally, all SAEs must be reported to the institutional review board (IRB) per the IRB's requirements.

Those SAEs that are considered both serious and unexpected and related to the study drug are subject to expedited reporting. An "unexpected AE" is any AE where the nature or severity is not consistent with the current investigator brochure (IB) or if an IB is not required or available, the specificity or severity is not consistent with the provided risk information.

Unexpected fatal or life-threatening SAEs related to the study drug must be reported by the Sponsor to the appropriate regulatory authority in an expedited manner (ie, first report within 7 days of first knowledge by the Sponsor). The Sponsor will provide a final written report to that authority within 15 days of initial receipt of information on the event. The Sponsor or the Sponsor's representative will also inform all participating Investigators of the SAE.

Unexpected SAEs that are not fatal or life-threatening must be reported by the Sponsor to the appropriate regulatory authority as soon as possible but no later than 15 calendar days after first knowledge of the SAE by the Sponsor. The Sponsor or the Sponsor's representative also informs all participating Investigators of the SAE.

Subjects withdrawn from the study due to any SAE will be followed until the SAE is resolved or medically stable. Record all SAEs, regardless of severity and whether or not related to the study medication, on the appropriate page of the CRF.

The Investigator must determine whether the seriousness of the event warrants removal of the subject from the study. He/she should, in any case, institute appropriate diagnostic and therapeutic measures and keep the subject under observation for as long as is medically indicated, or refer the subject to appropriate health professionals.

12.4. Pregnancy

Any pregnancy that occurs from the time the subject signs an ICF until 30 days after taking the final dose of study medication must be reported within 24 hours to the Sponsor or the Sponsor's representative and the subject should be terminated from the study. All pregnancies will be followed through to delivery of the infant. If the subject experiences a termination of the pregnancy, it should be reported as defined in Section 12.3.2.

12.5. Other Safety Parameters and Related Information

Additional safety parameters (laboratory tests, 12-lead ECGs, physical examinations, and vital signs), and concomitant medications are collected as shown in the Schedule of Assessments in Table 4 and evaluated over the course of the study. Clinical laboratory studies are listed in Appendix E.

13. STATISTICS

A comprehensive Statistical Analysis Plan (SAP) will be finalized before unblinding of the data. All statistical tests will be conducted using 5% level of significance and will be 2-sided. No multiplicity adjustment will be made for the secondary measures.

13.1. Sample Size Estimation

Part 1 of this study is a randomized, double-blind, placebo-controlled, 2-period, crossover outpatient study with a 6-week placebo run-in period.

Approximately 393 subjects will be enrolled to randomize 264 so that at least 180 subjects will need to complete both double-blind treatment periods. With the 5:1 (high dose:low dose) randomization ratio for each of the 2 weight strata, it is estimated that 150 high-dose subjects will need to complete both double-blind treatment periods and 30 subjects randomized to the lower dose level will need to complete both double-blind treatment periods.

The sample size is based on detecting a difference in the percentage of subjects treated with a high dose (2.5 mg in the <50 kg weight stratum and 5 mg in the ≥50 kg weight stratum) who are pain free at 2 hours between ZNS and placebo. In this crossover trial, 150 high-dose-treated subjects completing both treatment periods will be adequate to detect a clinically relevant difference of 0.11 in the percentage of subjects who are pain free at 2 hours between ZNS and placebo as statistically significant (0.05, two tailed) with at least 90% power assuming a standard deviation of 0.4 (Wang and Chow 2007).

Approximately 30 additional subjects will be required to complete treatment in both periods in the low dose level (1 mg in the <50 kg weight stratum and 2.5 mg in the ≥50 kg weight stratum). The data from the low dose level will be summarized to explore dose-relationship response.

A subject will be considered as having completed the study if the subject:

- administers or is administered study drug during each treatment period, and
- completes an assessment of headache pain intensity rating immediately prior to treatment (0 hours) and at 2 hours post-dose.

Based on other migraine crossover studies, dropout rates during the placebo run-in period ranged from 12% to 50% (Ho et al 2012, Lewis et al 2007, and CSR for Study D1220C00001). Following randomization, dropout rates varied between 20% and 35% (Ahonen et al 2006 and Lewis et al 2007). Based on this, approximately 393 subjects will be enrolled into the placebo run-in period to randomize 264 so that at least 180 subjects complete both double-blind treatment periods. This allows for approximately 32% dropout at each stage. With the 5:1 randomization, of the 180 completing subjects, it is estimated that 150 (83%) will be in a high dose group.

Approximately 100 subjects who complete the double-blind crossover phase will enter the 6 month OLE to enable at least 50 subjects to complete at least 6 months treating on average at least one migraine attack per month (treating up to 4 migraine attacks per month) with ZNS. Part 2 of the study is an OLE with subjects who successfully complete Part 1 of the study.

13.2. Demographics and Baseline Characteristics

The demographics and baseline characteristics will be tabulated and summarized at screening, placebo run-in, and randomization for Part 1. For Part 2, the demographics and other characteristics will be summarized at entry of the OLE (Visit 4).

13.3. Analysis of Efficacy Data

13.3.1. Primary Efficacy Endpoint

Pain-free status at 2-hour time point for the high dose is the primary efficacy endpoint to evaluate the efficacy of ZNS compared to placebo. Pain-free status is defined as a reduction in the headache pain intensity rating from moderate (2) or severe (3) pain to no pain (0).

The primary efficacy endpoint will be analyzed using Generalized Estimating Equations (GEE) methods. The model will include treatment, period, weight, and baseline headache pain intensity. The results of the analysis will be presented in terms of odds ratio for the treatment effect and the corresponding 95% confidence interval.

For the primary efficacy endpoint analysis, all subjects who have the 2-hour time point assessment for both treatment periods (Section 13.1) will be included in the analysis.

Following analysis will be conducted as corroborative evidence:

- Perform the Cochran-Mantel-Haenszel (CMH) test stratified by center using the data from the first period. Although this comparison will be underpowered, consistent trend with the analysis from the primary analysis will be considered as corroborative evidence. In addition to the CMH test, the estimate of the treatment difference and its 95% confidence interval will be presented for the first period.
- The percentage of patients achieving pain-free status by sequence and period will be summarized. This analysis will provide information on whether there is a differential dropout rate after each treatment and whether treatment by period interactions is evident.
- Conduct McNemar's test for each sequence to compare ZNS with placebo.

Additionally, as part of sensitivity analysis the following analyses will be conducted on the evaluable population:

- Subjects who have at least one post-dose pain intensity assessment in both treatment periods but are missing the 2-hour headache pain intensity assessment will have the 2-hour headache intensity assessment imputed by carrying forward the last observation within that period.
- Subjects with the missing 2-hour time point assessment post-dose will be imputed as non-responders for the treatment period where the assessment is missing.
- In case the dropout rate during the second treatment period is high (>20%), the following sensitivity analysis will be conducted to examine the robustness of the primary analysis results for the primary efficacy endpoint.

- Single imputation analysis: Subjects who discontinued after Period 1 and did not have data for Period 2 would be treated as not achieving pain-free response at 2-hour time point in Period 2. The primary analysis method will be used with the imputed data.
- Multiple imputation analysis: The Period 2 data for subjects who discontinued after Period 1 will be imputed based on the likelihood of achieving pain-free status for each treatment. The likelihood of pain-free status for each treatment will be based on the Period 1 data.
- Tipping point analysis: Period 2 data for subjects who discontinue after Period 1 will be imputed with a penalty. The penalty will be gradually increased to evaluate at which level the conclusion of the analyses in terms of statistical significance is changed.

The sensitivity analysis with single and multiple imputations and tipping point analysis will be described in the statistical analysis plan.

13.3.2. Secondary Efficacy Endpoints

If the treatment difference between ZNS high dose is statistically significantly different from placebo, low dose will be compared to placebo in a similar fashion to the primary endpoint. The following secondary endpoints with binary response variables will be analyzed using GEE methods by dose levels.

1. Pain-free status at 2-hour time point for low dose level
2. Pain-free status at 30 minutes, 1-hour and 24-hour time point
3. Absence of associated migraine symptoms (photophobia, phonophobia, nausea) at 30 minutes and at 1, 2, and 24 hours post-dose
4. Headache response - defined as a reduction in moderate (2) or severe (3) pain to mild (1) or no (0) pain at 30 minutes and at 1, 2, and 24 hours post-dose
5. Incidence of use of rescue medication up to 24 hours post-dose
6. Incidence of headache recurrence during 2 to 24 hours post treatment for the subset of subjects who attained a 2-hour pain-free response
7. Incidence of headache recurrence during 2 to 24 hours post treatment for the subset of subjects who attained a 2-hour headache response
8. Sustained headache response and sustained pain free response 2 to 24 hours post-dose.

The model will include treatment, period, weight, and baseline headache pain intensity. The results of the analysis will be presented in terms of odds ratio for the treatment effect and the corresponding 95% confidence interval.

All subjects who complete the study (Section 13.1) will be included in the analysis. No data will be imputed for the 24-hour time point (observed cases only).

Time to use of rescue medication for the two treatments will be analyzed using the Cox Proportional Hazards model with treatment, period, sequence, weight, and baseline headache

pain intensity in the model. Time to use will graphically presented using the Kaplan-Meier estimation.

13.3.3. Open-label Extension (OLE) Clinical Assessment Endpoints

The pain-free status at the 2-hour time point for each migraine attack that reached moderate to severe headache pain intensity and was treated with ZNS will be summarized at each visit to allow for clinical assessment of the maintenance of effect.

Additionally, the PedMIDAS data collected at randomization (Part 1) and at the last visit during OLE will be summarized.

13.4. Population Analysis and Handling of Dropouts

Safety Population: All subjects treated with any study medication including placebo run-in.

All Completers Population: All subjects treated with study drug during both periods and completed the assessment of 2-hour headache pain intensity rating during each period.

All Evaluable Population: All subjects treated with study drug during each period and complete at least one assessment of headache pain intensity rating at the following time points: 30 minutes, 1 hour, or 2 hours.

All Observed Cases: All observed data obtained on subjects who receive any study drug post randomization.

The trial design requires at least 150 high-dose subjects and 30 low-dose subjects to complete the study. However, if more than 20% of the subjects do not complete the study (ie, subjects completed treatment in Period 1 but not Period 2), sensitivity analyses to explore the impact of missing data and potential unbalances between sequences may be carried out if deemed necessary. As part of sensitivity analysis the following analyses will be conducted:

- Last observation will be carried forward (LOCF) for the endpoint if subjects who have at least one post-dose assessment in both treatment periods but are missing the 2-hour assessment (photophobia, phonophobia and nausea) within that period.
- Subjects with the missing 2-hour time point assessment (photophobia, phonophobia and nausea) post-dose will be imputed as non-responders for the treatment period where the assessment is missing.

13.5. Safety Analysis

The safety analysis will include all subjects who receive at least 1 dose of study drug. No formal statistical analyses will be made on the safety data.

Reported AEs will be coded to standard terms using a standard dictionary (Medical Dictionary for Regulatory Activities [MedDRA]). Number and incidence rates for AEs in each treatment will be tabulated. The relationship of the AE to study drug will also be summarized. Adverse events that lead to early discontinuation of subjects from the study will also be tabulated for each treatment. Each AE (based on preferred terminology) is counted only once for a given subject for each treatment. If the same AE occurred on multiple occasions with different severity levels and different relationships, the AE will be counted once at the highest severity level and with the

least complimentary relationship. If two or more AEs were reported as a unit, the individual terms will be reported as separate AEs.

The secondary safety variables including early termination data, laboratory test data, physical examination data, vital signs, ECGs, and concomitant medications will be tabulated. Clinical laboratory values are to be summarized by visit, including change from baseline. Medically significant laboratory values outside of normal reference ranges will also be tabulated and assessed.

14. ADMINISTRATIVE PROCEDURES

14.1. Guidelines for Good Clinical Practice

This study will be conducted in accordance with principles of Good Clinical Practice (GCP) as promulgated by the ICH. Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of human subjects are protected under current ethical principles, and that the clinical trial data are credible. Current GCP standards may be found in ICH Guidance E6 (Good Clinical Practice: Consolidated Guidance). This guidance describes the principles of GCP and the obligations of the institutional review board (IRB), the Investigator and the Sponsor in conducting this study in accordance with those principles.

14.2. Institutional Review Board Approval

The review of this protocol by an IRB and the performance of all aspects of the study, including the methods used for obtaining informed consent, must be in accordance with principles enunciated in the ICH and GCP Guidelines and by the appropriate regulatory authorities.

The Investigator is responsible for preparing documents for submission to the relevant IRB and obtaining written approval for this study. Institutional Review Board approval must be obtained prior to the initiation of the study. The Investigator's continued participation in the study is contingent on renewing approval with the IRB at least annually.

14.3. Informed Consent

Site personnel should prepare an Informed Consent Form (ICF) incorporating the necessary elements of consent. The ICF is to be approved by Impax or designee prior to submission to the IRB. The Investigator or his/her staff must explain the nature of the investigation and the risks involved to each subject prior to screening, and obtain a signed ICF. The subject should also be informed that he/she is free to voluntarily withdraw from the study at any time.

14.4. Study Monitoring

Impax representatives or designees will conduct site visits to the investigational facilities for the purpose of monitoring the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relevant to study conduct. The Investigator must permit access to such records if a regulatory or compliance audit is required.

14.5. Protocol Amendments

All amendments to the protocol must be documented in writing, reviewed and approved by the Sponsor and Investigator, and submitted to the IRB for approval prior to implementation. If the protocol amendment substantially alters the study design or potential risk to the subject, a new

written ICF for continued participation in the study must be obtained from each subject affected by the change.

14.6. Termination of Study

The Sponsor has the right to terminate this study and remove all study material from the site at any time for medical or administrative reasons. In this event, the Sponsor will endeavor to give adequate notice to allow safe withdrawal of subjects from the study.

14.7. Case Report Forms

Site personnel should collect and record data for the study as source documents, and transcribe the data into the CRF.

The Investigator must ensure that complete data for the clinical study are collected and accurately documented in the appropriate sections of the CRF and adequately supported by the appropriate source documentation. In addition, it is the Investigator's responsibility to provide signatures where requested indicating concurrence with data in the CRF.

14.8. Investigator's Final Conduct Report

At the completion of the study, the Investigator must provide Impax a copy of the final conduct report that was submitted to their IRB, including a review of AEs.

14.9. Records Retention

International Conference on Harmonization, GCP, and US FDA guidelines require that essential documents be retained until at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

However, the essential documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. Records should never be destroyed without written approval from the Sponsor.

If an Investigator leaves the institution, he/she must transfer responsibilities for record retention to another individual willing to accept them. The Investigator must notify the Sponsor in writing of the transfer of study documents before the transfer of the study documents.

15. PUBLICATION POLICY

Study results may not be published without prior written approval from Impax.

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17. APPENDICES

APPENDIX A. INTERNATIONAL HEADACHE SOCIETY REVISED CRITERIA (ICHD-3B)

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The International Classification of Headache Disorders, 3rd edition (beta version)

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Translations

The International Headache Society expressly permits translations of all or parts of ICHD-3 beta for purposes of field testing and/or education, but will not endorse them. Endorsements may be given by member national societies; where these exist, such endorsement should be sought. All translations are required to be registered with the International Headache Society. Before embarking upon translation, prospective translators are advised to enquire whether a translation exists already. All translators should be aware of the need to use rigorous translation protocols. Publications reporting studies making use of translations of all or any part of ICHD-3 beta should include a brief description of the translation process, including the identities of the translators (of whom there should always be more than one).

1. Migraine

1.1 Migraine without aura
1.2 Migraine with aura
  1.2.1 Migraine with typical aura
    1.2.1.1 Typical aura with headache
    1.2.1.2 Typical aura without headache
  1.2.2 Migraine with brainstem aura
  1.2.3 Hemiplegic migraine
    1.2.3.1 Familial hemiplegic migraine (FHM)
      1.2.3.1.1 Familial hemiplegic migraine type 1
      1.2.3.1.2 Familial hemiplegic migraine type 2
      1.2.3.1.3 Familial hemiplegic migraine type 3
      1.2.3.1.4 Familial hemiplegic migraine, other loci
    1.2.3.2 Sporadic hemiplegic migraine
  1.2.4 Retinal migraine
1.3 Chronic migraine
1.4 Complications of migraine
  1.4.1 Status migrainosus
  1.4.2 Persistent aura without infarction
  1.4.3 Migrainous infarction
  1.4.4 Migraine aura-triggered seizure
1.5 Probable migraine
  1.5.1 Probable migraine without aura
  1.5.2 Probable migraine with aura
1.6 Episodic syndromes that may be associated with migraine
  1.6.1 Recurrent gastrointestinal disturbance
    1.6.1.1 Cyclical vomiting syndrome
    1.6.1.2 Abdominal migraine
  1.6.2 Benign paroxysmal vertigo
  1.6.3 Benign paroxysmal torticollis

Coded elsewhere:
Migraine-like headache secondary to another disorder (*symptomatic migraine*) is coded as a secondary headache attributed to that disorder.

General comment

Primary or secondary headache or both?

When a new headache with the characteristics of migraine occurs for the first time in close temporal relation to another disorder known to cause headache, or fulfils other criteria for causation by that disorder, the new headache is coded as a secondary headache attributed to the causative disorder. When *pre-existing* migraine becomes *chronic* in close temporal relation to such a causative disorder, both the initial migraine diagnosis and the secondary diagnosis should be given. 8.2 *Medication-overuse headache* is a particularly important example of this: both the episodic or chronic migraine diagnosis and the diagnosis 8.2 *Medication-overuse headache* should be given when medication overuse is present. When *pre-existing* migraine is made significantly worse (usually meaning a two-fold or greater increase in frequency and/or severity) in close temporal relation to such a causative disorder, both the initial migraine diagnosis and the secondary headache diagnosis should be given, provided that there is good evidence that the disorder can cause headache.

Introduction

Migraine is a common disabling primary headache disorder. Epidemiological studies have documented its high prevalence and high socio-economic and personal impacts. In the *Global Burden of Disease Survey 2010*, it was ranked as the third most prevalent disorder and seventh-highest specific cause of disability worldwide.

Migraine has two major subtypes. 1.1 *Migraine without aura* is a clinical syndrome characterized by headache with specific features and associated symptoms. 1.2 *Migraine with aura* is primarily characterized by the transient focal neurological symptoms that usually precede or sometimes accompany the headache. Some patients also experience a premonitory phase, occurring hours or days before the headache, and a headache resolution phase. Premonitory and resolution symptoms include hyperactivity, hypoactivity, depression, cravings for particular foods, repetitive yawning, fatigue and neck stiffness and/or pain.

When a patient fulfils criteria for more than one subtype of migraine, all subtypes should be diagnosed and coded. For example, a patient who has frequent attacks with aura but also some attacks without aura should be coded as 1.2 *Migraine with aura* and 1.1 *Migraine without aura*. Attacks of either type are included in the diagnostic criteria for 1.3 *Chronic migraine*.

1.1 Migraine without aura

Previously used terms:
Common migraine; hemicrania simplex.

Description:
Recurrent headache disorder manifesting in attacks lasting 4-72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia.

Diagnostic criteria:

A. At least five attacks[1] fulfilling criteria B–D
B. Headache attacks lasting 4–72 hours (untreated or unsuccessfully treated)[2,3]
C. Headache has at least two of the following four characteristics:
   1. unilateral location
   2. pulsating quality
   3. moderate or severe pain intensity
   4. aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
D. During headache at least one of the following:
   1. nausea and/or vomiting
   2. photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis.

Notes:

1. One or a few migraine attacks may be difficult to distinguish from symptomatic migraine-like attacks. Furthermore, the nature of a single or a few attacks may be difficult to understand. Therefore, at least five attacks are required. Individuals who otherwise meet criteria for 1.1 *Migraine without aura* but have had fewer than five attacks, should be coded 1.5.1 *Probable migraine without aura.*
2. When the patient falls asleep during a migraine attack and wakes up without it, duration of the attack is reckoned until the time of awakening.
3. In children and adolescents (aged under 18 years), attacks may last 2–72 hours (the evidence for untreated durations of less than 2 hours in children has not been substantiated).

Comments:

Migraine headache in children and adolescents (aged under 18 years) is more often bilateral than is the case in adults; unilateral pain usually emerges in late adolescence or early adult life. Migraine headache is usually frontotemporal. Occipital headache in *children* is rare and calls for diagnostic caution. A subset of otherwise typical patients have facial location of pain, which is called 'facial migraine' in the literature; there is no evidence that these patients form a separate subgroup of migraine patients. In young children, photophobia and phonophobia may be inferred from their behaviour. Migraine attacks can be associated with cranial autonomic symptoms and symptoms of cutaneous allodynia.

Migraine without aura often has a menstrual relationship. ICHD-3 beta offers criteria for A1.1.1 *Pure menstrual migraine* and A1.1.2 *Menstrually related migraine*, but in the Appendix because of uncertainty over whether they should be regarded as separate entities.

Very frequent migraine attacks are now distinguished as 1.3 *Chronic migraine*. When there is associated medication overuse, both diagnoses, 1.3 *Chronic migraine* and 8.2 *Medication-overuse headache*, should be applied. 1.1 *Migraine without aura* is the disease most prone to accelerate with frequent use of symptomatic medication.

Regional cerebral blood flow imaging shows no changes suggestive of cortical spreading depression (CSD) during attacks of migraine without aura, although blood flow changes may occur in the brainstem, as may cortical changes secondary to pain activation. This contrasts with the pathognomonic spreading oligaemia of migraine with aura. Although the bulk of the literature suggests that CSD does not occur in migraine without aura, some recent studies disagree. Furthermore, it has been suggested that glial waves or other cortical phenomena may be involved in migraine without aura. The messenger molecules nitric oxide (NO), 5-hydroxytryptamine (5-HT) and calcitonin gene-related peptide (CGRP) are involved. Although the disease was previously regarded as primarily vascular, the importance of sensitization of pain pathways, and the possibility that attacks may originate in the central nervous system, have gained increasing attention over recent decades. At the same time, the circuitry of migraine pain, the trigeminovascular system, and several aspects of its neurotransmission peripherally and in the trigeminal nucleus caudalis, the central mesencephalic grey and the thalamus, have been recognized. New highly receptor-specific acute medications such as the triptans, which are $5HT_{1B/D}$ receptor agonists, $5\text{-}HT_{1F}$ receptor agonists and CGRP receptor antagonists have demonstrated efficacy in the acute treatment of attacks. Because of their high receptor-specificity, their mechanism of action provides new insight into migraine mechanisms. It is now clear that migraine without aura is a neurobiological disorder; clinical as well as basic neuroscience has advanced our knowledge of migraine mechanisms, and continues to do so.

1.2 Migraine with aura

Previously used terms:

Classic or classical migraine; ophthalmic, hemiparaesthetic, hemiplegic or aphasic migraine; migraine accompagnée; complicated migraine.

Description:
Recurrent attacks, lasting minutes, of unilateral fully reversible visual, sensory or other central nervous system symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms.

Diagnostic criteria:

A. At least two attacks fulfilling criteria B and C
B. One or more of the following fully reversible aura symptoms:
   1. visual
   2. sensory
   3. speech and/or language
   4. motor
   5. brainstem
   6. retinal
C. At least two of the following four characteristics:
   1. at least one aura symptom spreads gradually over ≥5 minutes, and/or two or more symptoms occur in succession
   2. each individual aura symptom lasts 5-60 minutes[1]
   3. at least one aura symptom is unilateral[2]
   4. the aura is accompanied, or followed within 60 minutes, by headache
D. Not better accounted for by another ICHD-3 diagnosis, and transient ischaemic attack has been excluded.

Notes:

1. When, for example, three symptoms occur during an aura, the acceptable maximal duration is 3×60 minutes. Motor symptoms may last up to 72 hours.
2. Aphasia is always regarded as a unilateral symptom; dysarthria may or may not be.

Comments:
The aura is the complex of neurological symptoms that occurs usually before the headache of 1.2 *Migraine with aura*, but it may begin after the pain phase has commenced, or continue into the headache phase.

Visual aura is the most common type of aura, occurring in over 90% of patients with 1.2 *Migraine with aura*, at least in some attacks. It often presents as a fortification spectrum: a zigzag figure near the point of fixation that may gradually spread right or left and assume a laterally convex shape with an angulated scintillating edge, leaving absolute or variable degrees of relative scotoma in its wake. In other cases, scotoma without positive phenomena may occur; this is often perceived as being of acute onset but, on scrutiny, usually enlarges gradually. In children and adolescents, less typical bilateral visual symptoms occur that may represent an aura. A visual aura rating scale with high specificity and sensitivity has been developed and validated.

Next in frequency are sensory disturbances, in the form of pins and needles moving slowly from the point of origin and affecting a greater or smaller part of one side of the body, face and/or tongue. Numbness may occur in its wake, but numbness may also be the only symptom.

Less frequent are speech disturbances, usually aphasic but often hard to categorize.

When the aura includes motor weakness, the disorder should be coded as 1.2.3 *Hemiplegic migraine* or one of its subforms.

Aura symptoms of these different types usually follow one another in succession, beginning with visual, then sensory, then aphasic; but the reverse and other orders have been noted. The accepted duration for most aura symptoms is 1 hour, but motor symptoms are often longer lasting.

Patients often find it hard to describe their aura symptoms, in which case they should be instructed to time and record them prospectively. The clinical picture then becomes clearer. Common mistakes are incorrect reports of lateralization, of sudden rather than gradual onset and of monocular rather than homonymous visual disturbances, as well as of duration of aura and mistaking sensory loss for weakness. After an initial consultation, use of an aura diary may clarify the diagnosis.

Many patients who have migraine attacks with aura also have attacks without aura; they should be coded as both 1.2 *Migraine with aura* and 1.1 *Migraine without aura*.

Premonitory symptoms may begin hours or a day or two before the other symptoms of a migraine attack (with or without aura). They include various combinations of fatigue, difficulty in concentrating, neck stiffness, sensitivity to light and/or sound, nausea, blurred vision, yawning and pallor. The terms 'prodrome' and 'warning symptoms' are best avoided, because they are often mistakenly used to include aura.

Migraine aura is sometimes associated with a headache that does not fulfil criteria for 1.1 *Migraine without aura*, but this is still regarded as a migraine headache because of its relation to the aura. In other cases, migraine aura may occur without headache.

Before or simultaneously with the onset of aura symptoms, regional cerebral blood flow is decreased in the cortex corresponding to the clinically affected area and often over a wider area. Blood flow reduction usually starts posteriorly and spreads anteriorly, and is usually above the ischaemic threshold. After 1 to

several hours, gradual transition into hyperaemia occurs in the same region. Cortical spreading depression of Leão is the likely underlying mechanism.

Systematic studies have demonstrated that many patients with visual aura occasionally have symptoms in the extremities and/or speech symptoms. Conversely, patients with symptoms in the extremities and/or speech or language symptoms almost always also experience visual aura symptoms at least during some attacks. A distinction between migraine with visual aura, migraine with hemiparaesthetic aura and migraine with speech and/or language aura is probably artificial, and therefore is not recognized in this classification. They are all coded as 1.2.1 *Migraine with typical aura*. Patients with aura symptoms arising from the brainstem are coded as 1.2.2 *Migraine with brainstem aura*, but they almost always have additional typical aura symptoms. Patients with 1.2.3 *Hemiplegic migraine* have motor weakness, and this is classified as a separate subform because of genetic and pathophysiological differences from migraine with typical aura. Such patients often have brainstem symptoms in addition.

The previously defined syndromes, *migraine with prolonged aura* and *migraine with acute-onset aura*, have been abandoned. The great majority of patients with such attacks have other attacks that fulfil criteria for one of the recognized subforms of 1.2 *Migraine with aura*, and should be coded to that diagnosis. The rest should be coded to 1.5.2 *Probable migraine with aura*, specifying the atypical feature (prolonged aura or acute onset aura) in parenthesis. The diagnosis is usually evident after a careful history alone, although there are rare secondary mimics including carotid dissection, arteriovenous malformation and seizure.

1.2.1 Migraine with typical aura

Description:
Migraine with aura in which aura consists of visual and/or sensory and/or speech/language symptoms, but no motor weakness, and is characterized by gradual development, duration of each symptom no longer than 1 hour, a mix of positive and negative features and complete reversibility.

Diagnostic criteria:

A. At least two attacks fulfilling criteria B and C
B. Aura consisting of visual, sensory and/or speech/language symptoms, each fully reversible, but no motor, brainstem or retinal symptoms
C. At least two of the following four characteristics:
   1. at least one aura symptom spreads gradually over ≥5 minutes, and/or two or more symptoms occur in succession
   2. each individual aura symptom lasts 5-60 minutes[1]
   3. at least one aura symptom is unilateral[2]
   4. the aura is accompanied, or followed within 60 minutes, by headache
D. Not better accounted for by another ICHD-3 diagnosis, and transient ischaemic attack has been excluded.

Notes:

1. When for example three symptoms occur during an aura, the acceptable maximal duration is 3×60 minutes.
2. Aphasia is always regarded as a unilateral symptom; dysarthria may or may not be.

1.2.1.1 Typical aura with headache

Description:
Migraine with typical aura in which aura is accompanied or followed within 60 minutes by headache with or without migraine characteristics.

Diagnostic criteria:

A. Fulfils criteria for 1.2.1 *Migraine with typical aura*
B. Headache, with or without migraine characteristics, accompanies or follows the aura within 60 minutes.

1.2.1.2 Typical aura without headache

Description:
Migraine with typical aura in which aura is neither accompanied nor followed by headache of any sort.

Diagnostic criteria:

A. Fulfils criteria for 1.2.1 *Migraine with typical aura*
B. No headache accompanies or follows the aura within 60 minutes.

Comments:
In some patients, a typical aura is always followed by migraine headache, but many patients have, in addition, attacks with aura followed by a less distinct headache or even without headache. A number of patients have, exclusively, 1.2.1.2 *Typical aura without headache*.

In the absence of headache fulfilling criteria for 1.1 *Migraine without aura*, the precise diagnosis of aura and its distinction from mimics that may signal serious

disease (e.g. transient ischaemic attack) becomes more difficult and often requires investigation. When aura occurs for the first time after age 40, when symptoms are exclusively negative (e.g. hemianopia) or when aura is prolonged or very short, other causes, particularly transient ischaemic attacks, should be ruled out.

1.2.2 Migraine with brainstem aura

Previously used terms:
Basilar artery migraine; basilar migraine; basilar-type migraine.

Description:
Migraine with aura symptoms clearly originating from the brainstem, but no motor weakness.

Diagnostic criteria:

A. At least two attacks fulfilling criteria B-D
B. Aura consisting of visual, sensory and/or speech/language symptoms, each fully reversible, but no motor[1] or retinal symptoms
C. At least two of the following brainstem symptoms:
   1. dysarthria
   2. vertigo
   3. tinnitus
   4. hypacusis
   5. diplopia
   6. ataxia
   7. decreased level of consciousness
D. At least two of the following four characteristics:
   1. at least one aura symptom spreads gradually over ≥5 minutes, and/or two or more symptoms occur in succession
   2. each individual aura symptom lasts 5-60 minutes[2]
   3. at least one aura symptom is unilateral[3]
   4. the aura is accompanied, or followed within 60 minutes, by headache
E. Not better accounted for by another ICHD-3 diagnosis, and transient ischaemic attack has been excluded.

Notes:

1. When motor symptoms are present, code as 1.2.3 *Hemiplegic migraine.*
2. When for example three symptoms occur during an aura, the acceptable maximal duration is 3×60 minutes.
3. Aphasia is always regarded as a unilateral symptom; dysarthria may or may not be.

Comments:
Originally the terms *basilar artery migraine* or *basilar migraine* were used but, as involvement of the basilar artery is unlikely, the term *migraine with brainstem aura* is preferred.

There are typical aura symptoms in addition to the brainstem symptoms during most attacks. Many patients who have attacks with brainstem aura also report other attacks with typical aura and should be coded for both 1.2.1 *Migraine with typical aura* and 1.2.2 *Migraine with brainstem aura.*

Many of the symptoms listed under criterion C may occur with anxiety and hyperventilation, and therefore are subject to misinterpretation.

1.2.3 Hemiplegic[1] migraine

Description:
Migraine with aura including motor weakness.

Diagnostic criteria:

A. At least two attacks fulfilling criteria B and C
B. Aura consisting of both of the following:
   1. fully reversible motor weakness
   2. fully reversible visual, sensory and/or speech/language symptoms
C. At least two of the following four characteristics:
   1. at least one aura symptom spreads gradually over ≥5 minutes, and/or two or more symptoms occur in succession
   2. each individual non-motor aura symptom lasts 5 60 minutes, and motor symptoms last <72 hours[2]
   3. at least one aura symptom is unilateral[3]
   4. the aura is accompanied, or followed within 60 minutes, by headache
D. Not better accounted for by another ICHD-3 diagnosis, and transient ischaemic attack and stroke have been excluded.

Notes:

1. The term *plegic* means paralysis in most languages, but most attacks are characterized by motor weakness.
2. In some patients, motor weakness may last weeks.
3. Aphasia is always regarded as a unilateral symptom; dysarthria may or may not be.

Comment:
It may be difficult to distinguish weakness from sensory loss.

1.2.3.1 Familial hemiplegic migraine (FHM)

Description:
Migraine with aura including motor weakness, and at least one first- or second-degree relative has migraine aura including motor weakness.

Diagnostic criteria:

A. Fulfils criteria for 1.2.3 *Hemiplegic migraine*
B. At least one first- or second-degree relative has had attacks fulfilling criteria for 1.2.3 *Hemiplegic migraine.*

Comments:
New genetic data have allowed a more precise definition of 1.2.3.1 *Familial hemiplegic migraine (FHM)* than was possible previously. Specific genetic subtypes have been identified: in FHM1 there are mutations in the CACNA1A gene (coding for a calcium channel) on chromosome 19; in FHM2 there are mutations in the ATP1A2 gene (coding for a K/Na-ATPase) on chromosome 1; and in FHM3 there are mutations in the SCN1A gene (coding for a sodium channel) on chromosome 2. There may be other loci not yet identified. When genetic testing is done, the genetic subtype (if discovered) should be specified at the fifth digit.

It has been shown that 1.2.3.1 *Familial hemiplegic migraine (FHM)* very often presents with brainstem symptoms in addition to the typical aura symptoms, and that headache almost always occurs. Rarely, during FHM attacks, disturbances of consciousness (sometimes including coma), confusion, fever and CSF pleocytosis can occur.

1.2.3.1 *Familial hemiplegic migraine (FHM)* may be mistaken for epilepsy and (unsuccessfully) treated as such. FHM attacks can be triggered by (mild) head trauma. In approximately 50% of FHM families, chronic progressive cerebellar ataxia occurs independently of the migraine attacks.

1.2.3.1.1 Familial hemiplegic migraine type 1 (FHM1)

Diagnostic criteria:

A. Fulfils criteria for 1.2.3.1 *Familial hemiplegic migraine*
B. A causative mutation on the CACNA1A gene has been demonstrated.

1.2.3.1.2 Familial hemiplegic migraine type 2 (FHM2)

Diagnostic criteria:

A. Fulfils criteria for 1.2.3.1 *Familial hemiplegic migraine*
B. A causative mutation on the ATP1A2 gene has been demonstrated.

1.2.3.1.3 Familial hemiplegic migraine type 3 (FHM3)

Diagnostic criteria:

A. Fulfils criteria for 1.2.3.1 *Familial hemiplegic migraine*
B. A causative mutation on the SCN1A gene has been demonstrated.

1.2.3.1.4 Familial hemiplegic migraine, other loci

Diagnostic criteria:

A. Fulfils criteria for 1.2.3.1 *Familial hemiplegic migraine*
B. Genetic testing has demonstrated no mutation on the CACNA1A, ATP1A2 or SCN1A genes.

1.2.3.2 Sporadic hemiplegic migraine

Description:
Migraine with aura including motor weakness, and no first- or second-degree relative has migraine aura including motor weakness.

Diagnostic criteria:

A. Fulfils criteria for 1.2.3 *Hemiplegic migraine*
B. No first- or second-degree relative fulfils criteria for 1.2.3 *Hemiplegic migraine.*

Comments:
Epidemiological studies have shown that sporadic cases occur with approximately the same prevalence as familial cases.

The attacks in 1.2.3.2 *Sporadic hemiplegic migraine* have the same clinical characteristics as those in 1.2.3.1 *Familial hemiplegic migraine*. Some apparently sporadic cases have known FHM mutations, and in some a first- or second-degree relative later develops hemiplegic migraine, thus completing fulfilment of the criteria for 1.2.3.1 *Familial hemiplegic migraine* and requiring a change of diagnosis.

Sporadic cases usually require neuroimaging and other tests to rule out other causes. A lumbar puncture may be necessary to rule out 7.3.5 *Syndrome of transient Headache and Neurological Deficits with cerebrospinal fluid Lymphocytosis (HaNDL)*.

1.2.4 Retinal migraine

Description:
Repeated attacks of monocular visual disturbance, including scintillations, scotomata or blindness, associated with migraine headache.

Diagnostic criteria:

A. At least two attacks fulfilling criteria B and C
B. Aura consisting of fully reversible monocular positive and/or negative visual phenomena (e.g. scintillations, scotomata or blindness) confirmed during an attack by either or both of the following:
   1. clinical visual field examination
   2. the patient's drawing (made after clear instruction) of a monocular field defect
C. At least two of the following three characteristics
   1. the aura spreads gradually over ≥5 minutes
   2. aura symptoms last 5-60 minutes
   3. the aura is accompanied, or followed within 60 minutes, by headache
D. Not better accounted for by another ICHD-3 diagnosis, and other causes of amaurosis fugax have been excluded.

Comments:
Some patients who complain of monocular visual disturbance in fact have hemianopia. Some cases without headache have been reported, but migraine cannot be ascertained as the underlying aetiology.

1.2.4 *Retinal migraine* is an extremely rare cause of transient monocular visual loss. Cases of permanent monocular visual loss associated with migraine have been described. Appropriate investigations are required to exclude other causes of transient monocular blindness.

1.3 Chronic migraine[1,2]

Description:
Headache occurring on 15 or more days per month for more than 3 months, which has the features of migraine headache on at least 8 days per month.

Diagnostic criteria:

A. Headache (tension-type-like and/or migraine-like) on ≥15 days per month for >3 months[2] and fulfilling criteria B and C
B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for 1.1 *Migraine without aura* and/or criteria B and C for 1.2 *Migraine with aura*
C. On ≥8 days per month for >3 months, fulfilling any of the following[3]:
   1. criteria C and D for 1.1 *Migraine without aura*
   2. criteria B and C for 1.2 *Migraine with aura*
   3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
D. Not better accounted for by another ICHD-3 diagnosis.

Notes:

1. The diagnosis of 1.3 *Chronic migraine* excludes the diagnosis of 2. *Tension-type headache* or its subtypes because tension-type-like headache is within the diagnostic criteria for 1.3 *Chronic migraine*.
2. The reason for singling out chronic from episodic migraine is that it is impossible to distinguish the individual episodes of headache in patients with such frequent or continuous headaches. In fact, the characteristics of the headache may change not only from day to day but even within the same day. It is extremely difficult to keep such patients medication-free in order to observe the natural history of the headache. In this situation, attacks with or without aura are both counted, as well as tension-type-like headaches. The most common cause of symptoms suggestive of chronic migraine is medication overuse, as defined under 8.2 *Medication-overuse headache*. Around 50% of patients apparently with 1.3 *Chronic migraine* revert to an episodic migraine subtype after drug withdrawal; such patients are in a sense wrongly diagnosed as 1.3 *Chronic migraine*. Equally, many patients apparently overusing medication do not improve after drug withdrawal, and the diagnosis of 8.2 *Medication-overuse headache* may in a sense be inappropriate (assuming that chronicity induced by drug overuse is always reversible). For these reasons, and because of the general rule, patients meeting criteria for 1.3 *Chronic migraine* and for 8.2 *Medication-overuse headache* should be given both diagnoses. After drug withdrawal, migraine will either revert to the episodic subtype or remain chronic, and be re-diagnosed accordingly; in the latter case, the diagnosis of 8.2 *Medication-overuse*

headache may be rescinded. In some countries, it is usual practice to diagnose 8.2 *Medication-overuse headache* only on discharge.
3. Characterization of frequently recurring headache generally requires a headache diary to record information on pain and associated symptoms day-by-day for at least 1 month. Sample diaries are available at http://www.i-h-s.org.

1.4 Complications of migraine

Comment:
Code separately for both the migraine subtype and for the complication.

1.4.1 Status migrainosus

Description:
A debilitating migraine attack lasting for more than 72 hours.

Diagnostic criteria:

A. A headache attack fulfilling criteria B and C
B. Occurring in a patient with 1.1 *Migraine without aura* and/or 1.2 *Migraine with aura*, and typical of previous attacks except for its duration and severity
C. Both of the following characteristics:
   1. unremitting for >72 hours[1]
   2. pain and/or associated symptoms are debilitating[2]
D. Not better accounted for by another ICHD-3 diagnosis.

Notes:

1. Remissions of up to 12 hours because of medication or sleep are accepted.
2. Milder cases, not meeting criterion C2, are coded 1.5.1 *Probable migraine without aura.*

Comments:
Headache with the features of 1.4.1 *Status migrainosus* may often be caused by medication overuse. When headache in these circumstances meets the criteria for 8.2 *Medication-overuse headache*, code for 1.3 *Chronic migraine* and 8.2 *Medication-overuse headache* but not for 1.4.1 *Status migrainosus*. When overuse of medication is of shorter duration than 3 months, code for the appropriate migraine subtype(s) only.

1.4.2 Persistent aura without infarction

Description:
Aura symptoms persisting for 1 week or more without evidence of infarction on neuroimaging.

Diagnostic criteria:

A. Aura fulfilling criterion B
B. Occurring in a patient with 1.2 *Migraine with aura* and typical of previous auras except that one or more aura symptoms persists for ≥1 week
C. Neuroimaging shows no evidence of infarction
D. Not better accounted for by another ICHD-3 diagnosis.

Comments:
Persistent aura symptoms are rare but well documented. They are often bilateral and may last for months or years. The 1-week minimum in criterion B is based on the opinion of experts and should be formally studied.

Diagnostic work-up must distinguish 1.4.2 *Persistent aura without infarction* from 1.4.3 *Migrainous infarction*, and exclude symptomatic aura as a result of cerebral infarction of other causes. Attacks lasting more than 1 hour and less than 1 week and not fulfilling criteria for 1.2.1 *Migraine with typical aura* are coded 1.5.2 *Probable migraine with aura.*

1.4.3 Migrainous infarction

Description:
One or more migraine aura symptoms associated with an ischaemic brain lesion in the appropriate territory demonstrated by neuroimaging.

Diagnostic criteria:

A. A migraine attack fulfilling criteria B and C
B. Occurring in a patient with 1.2 *Migraine with aura* and typical of previous attacks except that one or more aura symptoms persists for >60 minutes
C. Neuroimaging demonstrates ischaemic infarction in a relevant area
D. Not better accounted for by another diagnosis.

Comments:
Ischaemic stroke in a migraine sufferer may be categorized as cerebral infarction of other cause coexisting with migraine, cerebral infarction of other cause presenting

with symptoms resembling migraine with aura, or cerebral infarction occurring during the course of a typical migraine with aura attack. Only the last fulfils criteria for 1.4.3 *Migrainous infarction*.

1.4.3 *Migrainous infarction* mostly occurs in the posterior circulation and in younger women

A two-fold increased risk of ischaemic stroke in patients with migraine with aura patients has been demonstrated in several population-based studies. However, it should be noted that these infarctions are not migrainous infarctions. The mechanisms of the increased risk of ischaemic stroke in migraine sufferers remain unclear; likewise, the relationship between frequency of aura and the nature of aura symptoms denoting the increase in risk is unknown. Most studies have shown a lack of association between migraine without aura and ischaemic stroke.

1.4.4 Migraine aura-triggered seizure

Description:
A seizure triggered by an attack of migraine with aura.

Diagnostic criteria:

A. A seizure fulfilling diagnostic criteria for one type of epileptic attack, and criterion B below
B. Occurring in a patient with 1.2 *Migraine with aura*, and during, or within 1 hour after, an attack of migraine with aura
C. Not better accounted for by another diagnosis.

Comment:
Migraine and epilepsy are prototypical examples of paroxysmal brain disorders. Although migraine-like headaches are quite frequently seen in the epileptic postictal period, sometimes a seizure occurs during or following a migraine attack. This phenomenon, sometimes referred to as *migralepsy*, is a rare event, originally described in patients with 1.2 *Migraine with aura*. Evidence for association with 1.1 *Migraine without aura* is still lacking.

1.5 Probable migraine

Previously used term:
Migrainous disorder.

Coded elsewhere:
Migraine-like headache secondary to another disorder (symptomatic migraine) is coded according to that disorder.

Description:
Migraine-like attacks missing one of the features required to fulfil all criteria for a subtype of migraine coded above, and not fulfilling criteria for another headache disorder.

Diagnostic criteria:

A. Attacks fulfilling all but one of criteria A-D for 1.1 *Migraine without aura*, or all but one of criteria A-C for 1.2 *Migraine with aura*
B. Not fulfilling ICHD-3 criteria for any other headache disorder
C. Not better accounted for by another ICHD-3 diagnosis.

Comment:
In making a headache diagnosis, attacks that fulfil criteria for both 2. *Tension-type headache* and 1.5 *Probable migraine* are coded as the former in accordance with the general rule that a definite diagnosis always trumps a probable diagnosis. However, in patients who already have a migraine diagnosis, and where the issue is to count the number of attacks they are having (e.g. as an outcome measure in a drug trial), attacks fulfilling criteria for 1.5 *Probable migraine* should be counted as migraine. The reason for this is that mild migraine attacks, or attacks treated early, often do not achieve all characteristics necessary for a migraine attack diagnosis but nevertheless respond to specific migraine treatments.

1.5.1 Probable migraine without aura

Diagnostic criteria:

A. Attacks fulfilling all but one of criteria A D for 1.1 *Migraine without aura*
B. Not fulfilling ICHD-3 criteria for any other headache disorder
C. Not better accounted for by another ICHD-3 diagnosis.

1.5.2 Probable migraine with aura

Diagnostic criteria:

A. Attacks fulfilling all but one of criteria A C for 1.2 *Migraine with aura* or any of its subforms
B. Not fulfilling ICHD-3 criteria for any other headache disorder
C. Not better accounted for by another ICHD-3 diagnosis.

1.6 Episodic syndromes that may be associated with migraine

Previously used terms:
Childhood periodic syndromes; periodic syndromes of childhood.

Comments:
This group of disorders occurs in patients who also have 1.1 *Migraine without aura* or 1.2 *Migraine with aura*, or who have an increased likelihood to develop either of these disorders. Although historically noted to occur in childhood, they may also occur in adults.

Additional conditions that may also occur in these patients include episodes of motion sickness and periodic sleep disorders including sleep walking, sleep talking, night terrors and bruxism.

1.6.1 Recurrent gastrointestinal disturbance

Previously used terms:
Chronic abdominal pain; functional abdominal pain; functional dyspepsia; irritable bowel syndrome; functional abdominal pain syndrome.

Description:
Recurrent episodic attacks of abdominal pain and/or discomfort, nausea and/or vomiting, occurring infrequently, chronically or at predictable intervals, that may be associated with migraine.

Diagnostic criteria:

A. At least five attacks with distinct episodes of abdominal pain and/or discomfort and/or nausea and/or vomiting
B. Normal gastrointestinal examination and evaluation
C. Not attributed to another disorder.

1.6.1.1 Cyclic vomiting syndrome

Description:
Recurrent episodic attacks of intense nausea and vomiting, usually stereotypical in the individual and with predictable timing of episodes. Attacks may be associated with pallor and lethargy. There is complete resolution of symptoms between attacks.

Diagnostic criteria:

A. At least five attacks of intense nausea and vomiting, fulfilling criteria B and C
B. Stereotypical in the individual patient and recurring with predictable periodicity
C. All of the following:
   1. nausea and vomiting occur at least four times per hour
   2. attacks last ≥1 hour and up to 10 days
   3. attacks occur ≥1 week apart
D. Complete freedom from symptoms between attacks
E. Not attributed to another disorder.[1]

Note:

1. In particular, history and physical examination do not show signs of gastrointestinal disease.

Comments:
1.6.1.1 *Cyclic vomiting syndrome* is typically a self-limiting episodic condition occurring in childhood, with periods of complete normality between episodes. The cyclic nature is the hallmark, and is predictable.

This disorder was not included as a childhood periodic syndrome in ICHD-I, but it was in ICHD-II. The clinical features of this syndrome resemble those found in association with migraine headaches, and multiple threads of research over the last years have suggested that cyclic vomiting syndrome is a condition related to migraine.

1.6.1.2 Abdominal migraine

Description:
An idiopathic disorder seen mainly in children as recurrent attacks of moderate to severe midline abdominal pain, associated with vasomotor symptoms, nausea and vomiting, lasting 2 72 hours and with normality between episodes. Headache does not occur during these episodes.

Diagnostic criteria:

A. At least five attacks of abdominal pain, fulfilling criteria B D
B. Pain has at least two of the following three characteristics:
   1. midline location, periumbilical or poorly localized
   2. dull or 'just sore' quality
   3. moderate or severe intensity
C. During attacks, at least two of the following:
   1. anorexia
   2. nausea
   3. vomiting
   4. pallor

D. Attacks last 2-72 hours when untreated or unsuccessfully treated
E. Complete freedom from symptoms between attacks
F. Not attributed to another disorder.[1]

Note:

1. In particular, history and physical examination do not show signs of gastrointestinal or renal disease, or such disease has been ruled out by appropriate investigations.

Comments:
Pain of 1.6.1.2 *Abdominal migraine* is severe enough to interfere with normal daily activities.

In young children the presence of headache is often overlooked. A careful history of presence or absence of headache must be taken and, if headache or head pain during attacks is identified, a diagnosis of 1.1 *Migraine without aura* should be considered.

Children may find it difficult to distinguish anorexia from nausea. Pallor is often accompanied by dark shadows under the eyes. In a few patients, flushing is the predominant vasomotor phenomenon.

Most children with abdominal migraine will develop migraine headache later in life.

1.6.2 Benign paroxysmal vertigo

Description:
A disorder characterized by recurrent brief attacks of vertigo, occurring without warning and resolving spontaneously, in otherwise healthy children.

Diagnostic criteria:

A. At least five attacks fulfilling criteria B and C
B. Vertigo[1] occurring without warning, maximal at onset and resolving spontaneously after minutes to hours without loss of consciousness
C. At least one of the following associated symptoms or signs:
   1. nystagmus
   2. ataxia
   3. vomiting
   4. pallor
   5. fearfulness
D. Normal neurological examination and audiometric and vestibular functions between attacks
E. Not attributed to another disorder.

Note:

1. Young children with vertigo may not be able to describe vertiginous symptoms. Parental observation of episodic periods of unsteadiness may be interpreted as vertigo in young children.

Comments:
Posterior fossa tumours, seizures and vestibular disorders must be excluded.

The relationship between 1.6.2 *Benign paroxysmal vertigo* and A1.6.6 *Vestibular migraine* (see Appendix) needs to be further examined.

1.6.3 Benign paroxysmal torticollis

Description:
Recurrent episodes of head tilt to one side, perhaps with slight rotation, which remit spontaneously. The condition occurs in infants and small children, with onset in the first year.

Diagnostic criteria:

A. Recurrent attacks[1] in a young child, fulfilling criteria B and C
B. Tilt of the head to either side, with or without slight rotation, remitting spontaneously after minutes to days
C. At least one of the following associated symptoms or signs:
   1. pallor
   2. irritability
   3. malaise
   4. vomiting
   5. ataxia[2]
D. Normal neurological examination between attacks
E. Not attributed to another disorder.

Notes:

1. Attacks tend to recur monthly.
2. Ataxia is more likely in older children within the affected age group.

Comments:
The child's head can be returned to the neutral position during attacks: some resistance may be encountered, but can be overcome.

The differential diagnosis includes gastro-oesophageal reflux, idiopathic torsional dystonia and complex partial seizure, but particular attention must be paid to

the posterior fossa and craniocervical junction where congenital or acquired lesions may produce torticollis. These observations need further validation by patient diaries, structured interviews and longitudinal data collection.

1.6.3 *Benign paroxysmal torticollis* may evolve into 1.6.2 *Benign paroxysmal vertigo* or 1.2 *Migraine with aura* (particularly 1.2.2 *Migraine with brainstem aura*), or cease without further symptoms.

Bibliography

1.1 Migraine in general

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APPENDIX B. HEADACHE PAIN INTENSITY SCALE AND ASSOCIATED MIGRAINE SYMPTOMS

Headache Pain Intensity Scale – Please select one	
Intensity of your pain at time of this rating	☐ (0) None
	☐ (1) Mild
	☐ (2) Moderate
	☐ (3) Severe

Associated Migraine Symptoms	
Are you experiencing any of the following symptoms?	
Nausea	☐ Yes ☐ No
Sound Sensitivity[a]	☐ Yes ☐ No
Light Sensitivity[b]	☐ Yes ☐ No

[a] Phonophobia
[b] Photophobia

APPENDIX C. PEDIATRIC MIGRAINE DISABILITY ASSESSMENT (PEDMIDAS)

PedMIDAS

Headache Disability.

The following questions try to assess how much the headaches are affecting day-to-day activity. Your answers should be based on the last three months. There are no "right" or "wrong" answers so please put down your best guess.

1. How many full school days of school were missed in the last 3 months due to headaches? _____

2. How many partial days of school were missed in the last 3 months due to headaches (do not include full days counted in the first question)? _____

3. How many days in the last 3 months did you function at less than half your ability in school because of a headache (do not include days counted in the first two questions)? _____

4. How many days were you not able to do things at home (i.e., chores, homework, etc.) due to a headache? _____

5. How many days did you not participate in other activities due to headaches (i.e., play, go out, sports, etc.)? _____

6. How many days did you participate in these activities, but functioned at less than half your ability (do not include days counted in the 5th question)? _____

Total PedMIDAS Score _____

Headache Frequency _____

Headache Severity _____

Cincinnati Children's

APPENDIX D. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Children's Baseline/Screening

Version 6/23/10

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103-130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION				
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime**		**Past 6 Months**	
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you thought about being dead or what it would be like to be dead?*** ***Have you wished you were dead or wished you could go to sleep and never wake up?*** ***Do you ever wish you weren't alive anymore?*** If yes, describe:	**Yes** ☐	**No** ☐	**Yes** ☐	**No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you thought about doing something to make yourself not alive anymore?*** ***Have you had any thoughts about killing yourself?*** If yes, describe:	**Yes** ☐	**No** ☐	**Yes** ☐	**No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you thought about how you would do that or how you would make yourself not alive anymore (kill yourself)? What did you think about?*** If yes, describe:	**Yes** ☐	**No** ☐	**Yes** ☐	**No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***When you thought about making yourself not alive anymore (or killing yourself), did you think that this was something you might actually do?*** ***This is different from (as opposed to) having the thoughts but knowing you wouldn't do anything about it.*** If yes, describe:	**Yes** ☐	**No** ☐	**Yes** ☐	**No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you ever decided how or when you would make yourself not alive anymore/kill yourself? Have you ever planned out (worked out the details of) how you would do it?*** ***What was your plan?*** ***When you made this plan (or worked out these details), was any part of you thinking about actually doing it?*** If yes, describe:	**Yes** ☐	**No** ☐	**Yes** ☐	**No** ☐
INTENSITY OF IDEATION				
The following feature should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe		Most Severe	
Frequency ***How many times have you had these thoughts?*** ***Write response***_____ (1) Only one time (2) A few times (3) A lot (4) All the time (0) Don't know/Not applicable	____		____	

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Did you ever do anything to try to kill yourself or make yourself not alive anymore? What did you do?*** ***Did you ever hurt yourself on purpose? Why did you do that?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to make yourself not alive anymore when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons, not at all to end your life or kill yourself (like to make yourself feel better, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes No ☐ ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes No ☐ ☐
Has subject engaged in Self-Injurious Behavior, intent unknown?	Yes No ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but someone or something stopped you before you actually did anything? What did you do?*** If yes, describe:	Yes No ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but you changed your mind (stopped yourself) before you actually did anything? What did you do?*** If yes, describe:	Yes No ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you done anything to get ready to make yourself not alive anymore (to end your life or kill yourself)- like giving things away, writing a goodbye note, getting things you need to kill yourself?*** If yes, describe:	Yes No ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes No ☐ ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

 C-SSRS—Children's Baseline/Screening (Version 6/23/10) Page 2 of 2

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Children's Since Last Visit

Version 6/23/10

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you thought about being dead or what it would be like to be dead?*** ***Have you wished you were dead or wished you could go to sleep and never wake up?*** ***Do you wish you weren't alive anymore?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you thought about doing something to make yourself not alive anymore?*** ***Have you had any thoughts about killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you thought about how you would do that or how you would make yourself not alive anymore (kill yourself)? What did you think about?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***When you thought about making yourself not alive anymore (or killing yourself), did you think that this was something you might actually do?*** ***This is different from (as opposed to) having the thoughts but knowing you wouldn't do anything about it.*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you decided how or when you would make yourself not alive anymore/kill yourself? Have you planned out (worked out the details of) how you would do it?*** ***What was your plan?*** ***When you made this plan (or worked out these details), was any part of you thinking about actually doing it?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following feature should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** ***Write response***_____ (1) Only one time (2) A few times (3) A lot (4) All the time (0) Don't know/Not applicable	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Did you <u>do anything</u> to try to kill yourself or make yourself not alive anymore? What did you do?*** ***Did you hurt yourself on purpose? Why did you do that?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to make yourself not alive anymore when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons, <u>not at all</u> to end your life or kill yourself (like to make yourself feel better, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?** **Has subject engaged in Self-Injurious Behavior, intent unknown?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but someone or something stopped you before you actually did anything? What did you do?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but you changed your mind (stopped yourself) before you actually did anything? What did you do?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you done anything to get ready to make yourself not alive anymore (to end your life or kill yourself)- like giving things away, writing a goodbye note, getting things you need to kill yourself?*** If yes, describe:	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐
Completed Suicide:	**Yes No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

 C-SSRS—Children's Since Last Visit (Version 6/23/10) Page 2 of 2

APPENDIX E. CLINICAL LABORATORY TESTS

HEMATOLOGY

hemoglobin	% lymphocytes	absolute lymphocytes
hematocrit	% monocytes	absolute monocytes
red blood cell count	% basophils	absolute basophils
white blood cell count	% eosinophils	absolute eosinophils
% neutrophils	absolute neutrophils	platelet count

CHEMISTRY

sodium	calcium	indirect bilirubin
potassium	phosphorous	alkaline phosphatase
chloride	albumin	alanine aminotransferase (ALT, SGPT)
carbon dioxide	total protein	aspartate aminotransferase (AST, SGOT)
blood urea nitrogen (BUN)	uric acid	creatine phosphokinase
creatinine	total bilirubin	lactate dehydrogenase
glucose	direct bilirubin	

URINALYSIS

pH	glucose	leukocyte esterase
specific gravity	ketones	microscopic exam (RBC and WBC only when indicated)
blood	protein	

URINE DRUG TEST

amphetamines	cocaine metabolites	benzodiazepines
barbiturates	opiates	
cannabinoids	phencyclidines	

PREGNANCY TEST

Urine pregnancy test (to be completed on-site) for female subjects of childbearing potential.

APPENDIX F. ZOLMITRIPTAN NASAL SPRAY PRESCRIBING INFORMATION

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZOMIG Nasal Spray safely and effectively. See full prescribing information for ZOMIG Nasal Spray.

ZOMIG (zolmitriptan) nasal spray
INITIAL US APPROVAL: 1997

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	6/2015
Dosage and Administration, Dosing Information (2.1)	6/2015

----------INDICATIONS AND USAGE----------

ZOMIG Nasal Spray is a serotonin (5-HT)$_{1B/1D}$ receptor agonist (triptan) indicated for the acute treatment of migraine with or without aura in adults and pediatric patients 12 years and older (1)

Limitations of Use:
- Use only after a clear diagnosis of migraine has been established (1)
- Not intended for the prophylactic therapy of migraine (1)
- Not indicated for the treatment of cluster headache (1)
- Not recommended in patients with moderate to severe hepatic impairment (1)

----------DOSAGE AND ADMINISTRATION----------
- Recommended starting dose: 2.5 mg (2.1)
- Maximum single dose: 5 mg (2.1)
- May repeat dose after 2 hours if needed; not to exceed 10 mg in any 24-hour period (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Nasal Spray: 2.5 mg and 5 mg (3)

----------CONTRAINDICATIONS----------
- History of ischemic heart disease or coronary artery vasospasm (4)
- Symptomatic Wolff-Parkinson-White syndrome or other cardiac accessory conduction pathway disorders (4)
- History of stroke, transient ischemic attack, or hemiplegic or basilar migraine (4)
- Peripheral Vascular Disease (4)
- Ischemic bowel disease (4)
- Uncontrolled hypertension (4)
- Recent (within 24 hours) use of another 5-HT$_1$ agonist (e.g., another triptan) or of an ergot-type medication (4)
- MAO-A inhibitor used in past 2 weeks (4)
- Hypersensitivity to ZOMIG (4)

----------WARNINGS AND PRECAUTIONS----------
- Myocardial Ischemia, Myocardial Infarction, and Prinzmetal's Angina: Perform cardiac evaluation in patients with multiple cardiovascular risk factors (5.1)
- Arrhythmias: Discontinue dosing if occurs (5.2)
- Chest/throat/neck/jaw pain, tightness, pressure, or heaviness: Generally not associated with myocardial ischemia; evaluate for coronary artery disease in patients at high risk (5.3)
- Cerebral hemorrhage, subarachnoid hemorrhage, and stroke: Discontinue dosing if occurs (5.4)
- Gastrointestinal ischemic events, peripheral vasospastic reactions: Discontinue dosing if occurs (5.5)
- Medication Overuse Headache: Detoxification may be necessary (5.6)
- Serotonin syndrome: Discontinue dosing if occurs (5.7, 7.5)
- Increase in blood pressure: very rarely associated with significant events (5.8)

----------ADVERSE REACTIONS----------

The most common adverse reactions (≥ 5% and > placebo) were:
- Adults: unusual taste, paresthesia, dizziness, and hyperesthesia (6.1)
- Pediatrics: unusual taste (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Impax Laboratories at 1-877-994-6729 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

If co-administered with cimetidine: Maximum single dose of 2.5 mg, not to exceed 5 mg in any 24-hour period (2.3, 7.4)

----------USE IN SPECIFIC POPULATIONS----------

Pregnancy: Based on animal data, may cause fetal harm (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 6/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZOMIG Nasal Spray is indicated for the acute treatment of migraine with or without aura in adults and pediatric patients 12 years of age and older.

Limitations of Use

- Only use ZOMIG if a clear diagnosis of migraine has been established. If a patient has no response to ZOMIG treatment for the first migraine attack, reconsider the diagnosis of migraine before ZOMIG is administered to treat any subsequent attacks.
- ZOMIG is not indicated for the prevention of migraine attacks.
- Safety and effectiveness of ZOMIG have not been established for cluster headache.
- Not recommended in patients with moderate or severe hepatic impairment [*see Dosage and Administration (2.2)*].

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended starting dose for ZOMIG nasal spray in adult and pediatric patients 12 years of age and older is 2.5 mg. As the individual response to ZOMIG nasal spray may vary, the dose should be adjusted on an individual basis. The maximum recommended single dose of ZOMIG is 5 mg.

If the migraine has not resolved by 2 hours after taking ZOMIG, or returns after a transient improvement, another dose may be administered at least 2 hours after the previous dose.

The maximum daily dose should not exceed 10 mg in any 24-hour period.

The safety of ZOMIG in the treatment of an average of more than four headaches in a 30-day period has not been established.

2.2 Dosing in Patients with Hepatic Impairment

ZOMIG nasal spray is not recommended in patients with moderate to severe hepatic impairment because of increased zolmitriptan blood levels in these patients and elevation of blood pressure in some of these patients. The recommended dosage of ZOMIG nasal spray in patients with mild hepatic impairment is the same as for patients with normal hepatic function [*see Dosage and Administration (2.1), Warnings and Precautions (5.8), Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*].

2.3 Dosing in Patients taking Cimetidine

If ZOMIG is co-administered with cimetidine, limit the maximum single dose of ZOMIG to 2.5 mg, not to exceed 5 mg in any 24-hour period [*see Drug Interactions (7.4) and Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

Nasal Spray 2.5 mg and 5 mg.

4 CONTRAINDICATIONS

ZOMIG is contraindicated in patients with:

- Ischemic coronary artery disease (angina pectoris, history of myocardial infarction, or documented silent ischemia), other significant underlying cardiovascular disease, or coronary artery vasospasm including Prinzmetal's angina [*see Warnings and Precautions (5.1)*]
- Wolff-Parkinson-White Syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders [*see Warnings and Precautions (5.2)*]
- History of stroke, transient ischemic attack (TIA) or history of hemiplegic or basilar migraine because these patients are at higher risk of stroke [*see Warnings and Precautions (5.4)*]
- Peripheral vascular disease (PVD) [*see Warnings and Precautions (5.5)*]
- Ischemic bowel disease [*see Warnings and Precautions (5.5)*]
- Uncontrolled hypertension [*see Warnings and Precautions (5.8)*]
- Recent use (i.e., within 24 hours) of another 5-HT_1 agonist, ergotamine-containing medication, or ergot-type medication (such as dihydroergotamine or methysergide) [*see Drug Interactions (7.1, 7.3)*]
- Concurrent administration of an MAO-A inhibitor or recent discontinuation of a MAO-A inhibitor (that is within 2 weeks) [*see Drug Interactions (7.2) and Clinical Pharmacology (12.3)*]
- Known hypersensitivity to ZOMIG (angioedema and anaphylaxis seen) [*see Adverse Reactions (6.2)*]

5 WARNINGS AND PRECAUTIONS

5.1 Myocardial Ischemia, Myocardial Infarction, and Prinzmetal's Angina

ZOMIG is contraindicated in patients with ischemic or vasospastic coronary artery disease (CAD). There have been rare reports of serious cardiac adverse reactions, including acute myocardial infarction, occurring within a few hours following administration of ZOMIG. Some of these reactions occurred in patients without known CAD. 5-HT_1 agonists including ZOMIG may cause coronary artery vasospasm (Prinzmetal's Angina), even in patients without a history of CAD.

Perform a cardiovascular evaluation in triptan-naïve patients who have multiple cardiovascular risk factors (e.g., increased age, diabetes, hypertension, smoking, obesity, strong family history of CAD) prior to receiving ZOMIG. Do not administer ZOMIG if there is evidence of CAD or coronary artery vasospasm [*see Contraindications (4)*]. For patients with multiple cardiovascular risk factors who have a negative cardiovascular evaluation, consider administrating the first ZOMIG dose in a medically-supervised setting and performing an electrocardiogram (ECG) immediately following ZOMIG

administration. For such patients, consider periodic cardiovascular evaluation in intermittent long-term users of ZOMIG.

5.2 Arrhythmias

Life-threatening disturbances of cardiac rhythm including ventricular tachycardia and ventricular fibrillation leading to death have been reported within a few hours following the administration of 5-HT_1 agonists. Discontinue ZOMIG if these disturbances occur. Patients with Wolff-Parkinson-White Syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders should not receive ZOMIG [*see Contraindications (4)*].

5.3 Chest, Throat, Neck and/or Jaw Pain/Tightness/Pressure

As with other 5-HT_1 agonists, sensations of tightness, pain, pressure, and heaviness in the precordium, throat, neck, and jaw commonly occur after treatment with ZOMIG and is usually non-cardiac in origin. However, if a cardiac origin is suspected, patients should be evaluated. Patients shown to have CAD and those with Prinzmetal's variant angina should not receive 5-HT_1 agonists [*see Contraindications (4)*].

5.4 Cerebrovascular Events

Cerebral hemorrhage, subarachnoid hemorrhage, and stroke have occurred in patients treated with 5-HT_1 agonists, and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the 5-HT_1 agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. Discontinue ZOMIG if a cerebrovascular event occurs.

As with other acute migraine therapies, before treating headaches in patients not previously diagnosed as migraineurs, and in migraineurs who present with symptoms atypical for migraine, other potentially serious neurological conditions should be excluded. ZOMIG should not be administered to patients with a history of stroke or transient ischemic attack [*see Contraindications (4)*].

5.5 Other Vasospasm Reactions

5-HT_1 agonists, including ZOMIG, may cause non-coronary vasospastic reactions, such as peripheral vascular ischemia, gastrointestinal vascular ischemia and infarction (presenting with abdominal pain and bloody diarrhea), splenic infarction, and Raynaud's syndrome. In patients who experience symptoms or signs suggestive of vasospasm reaction following the use of any 5-HT_1 agonist, the suspected vasospasm reaction should be ruled out before receiving additional ZOMIG doses [*see Contraindications (4)*].

Reports of transient and permanent blindness and significant partial vision loss have been reported with the use of 5-HT_1 agonists. Since visual disorders may be part of a migraine attack, a causal relationship between these events and the use of 5-HT_1 agonists have not been clearly established.

5.6 Medication Overuse Headache

Overuse of acute migraine drugs (e.g. ergotamine, triptans, opioids, or a combination of drugs for 10 or more days per month) may lead to exacerbation of headache (medication overuse headache). Medication overuse headache may present as migraine-like daily headaches, or as a marked increase in frequency of migraine attacks. Detoxification of patients, including withdrawal of the overused drugs, and treatment of withdrawal symptoms (which often includes a transient worsening of headache) may be necessary.

5.7 Serotonin Syndrome

Serotonin syndrome may occur with triptans, including ZOMIG, particularly during co-administration with selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and MAO inhibitors [*see Drug Interactions (7.5)*]. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms usually rapidly occurs within minutes to hours of receiving a new or a greater dose of a serotonergic medication. ZOMIG treatment should be discontinued if serotonin syndrome is suspected [*see Drug Interactions (7.5) and Patient Counseling Information (17)*].

5.8 Increase in Blood Pressure

Significant elevations in systemic blood pressure have been reported in patients treated with 5-HT_1 agonists including patients without a history of hypertension. Very rarely these increases in blood pressure have been associated with significant clinical events. In healthy subjects treated with 5 mg of ZOMIG oral tablet, an increase of 1 and 5 mm Hg in the systolic and diastolic blood pressure, respectively, was seen. In a study of patients with moderate to severe liver impairment, 7 of 27 patients experienced 20 to 80 mm Hg elevations in systolic and/or diastolic blood pressure after a dose of 10 mg of ZOMIG oral tablet. As with all triptans, blood pressure should be monitored in ZOMIG-treated patients. ZOMIG is contraindicated in patients with uncontrolled hypertension [*see Contraindications (4)*].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of labeling:

- Myocardial Ischemia, Myocardial Infarction, and Prinzmetal's Angina [*see Warnings and Precautions (5.1)*]
- Arrhythmias [*see Warnings and Precautions (5.2)*]
- Chest and or Throat, Neck and Jaw Pain/Tightness/Pressure [*see Warnings and Precautions (5.3)*]
- Cerebrovascular Events [*see Warnings and Precautions (5.4)*]
- Other Vasospasm Reactions [*see Warnings and Precautions (5.5)*]
- Medication Overuse Headache [*see Warnings and Precautions (5.6)*]
- Serotonin Syndrome [*see Warnings and Precautions (5.7)*]
- Increase in Blood Pressure [*see Warnings and Precautions (5.8)*]

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Adults

Among 460 patients treating 1180 single attacks with ZOMIG nasal spray in a blinded placebo controlled trial (Study 1), there was a low withdrawal rate related to adverse reactions: 5 mg (1.3%), 2.5 mg (0%), and placebo (0.4%). None of the withdrawals were due to a serious event. One patient was withdrawn due to abnormal ECG changes from baseline that were incidentally found 23 days after the last dose of ZOMIG nasal spray.

The most common adverse reactions (≥ 5% and > placebo) in any dosage strength in clinical trials for ZOMIG nasal spray were: unusual taste, paresthesia, hyperesthesia, and dizziness. The incidence of adverse reactions was generally dose-related.

Table 1 lists the adverse reactions from the controlled clinical trial (Study 1) that occurred in ≥ 2% of patients in either the 2.5 or 5 mg ZOMIG nasal spray dose groups and with an incidence greater than placebo.

Table 1: Adverse reactions in a Placebo-Controlled Study in Adult Patients with Migraine (Study 1)

Body System Adverse Reaction	Placebo (N=228)	ZOMIG 2.5 mg (N=224)	ZOMIG 5 mg (N=236)
Atypical Sensations			
Hyperesthesia	0%	1%	5%
Paraesthesia	6%	5%	10%
Warm Sensation	2%	4%	0%
Ear/Nose/Throat			
Disorder/Discomfort of nasal cavity	2%	1%	3%
Pain and Pressure Sensations			
Pain Location Specified	1%	2%	4%
Throat Pain	1%	4%	4%
Throat Tightness	1%	<1%	2%
Digestive			
Dry Mouth	<1%	3%	2%
Nausea	1%	1%	4%

Body System Adverse Reaction	Placebo (N=228)	ZOMIG 2.5 mg (N=224)	ZOMIG 5 mg (N=236)
Neurological			
Dizziness	4%	6%	3%
Somnolence	2%	1%	4%
Other			
Unusual Taste	3%	17%	21%
Asthenia	1%	3%	3%

In Study 1, adverse reactions occurring in ≥ 1% and < 2% of patients in all attacks in either ZOMIG nasal spray dose group and with incidence greater than that of placebo were: abdominal pain, chills, throat pressure, facial edema, chest pressure, palpitation, dysphagia, arthralgia, myalgia, and depersonalization.

The incidence of adverse reactions in controlled clinical trials was not affected by gender, weight, or age of the patients (18-39 vs. 40-65 years of age), or presence of aura. There were insufficient data to assess the impact of race on the incidence of adverse reactions.

Local Adverse Reactions:
Among 460 patients using ZOMIG 2.5 mg or 5 mg in the controlled clinical trial, approximately 3% noted local irritation or soreness at the site of administration. Adverse reactions of any kind, perceived in the nasopharynx (which may include systemic effects of triptans) were severe in about 1% of patients and approximately 57% resolved in 1 hour. Nasopharyngeal examinations, in a subset of patients participating in two long term trials of up to one year duration, failed to demonstrate any clinically significant changes with repeated use of ZOMIG nasal spray.

All nasopharyngeal adverse reactions with an incidence of ≥ 2% of patients in any ZOMIG nasal spray dose groups are included in Table 1.

Other Adverse Reactions:
In the paragraphs that follow, the frequencies of less commonly reported adverse clinical reactions are presented. Because the reports include reactions observed in open and uncontrolled studies, the role of ZOMIG in their causation cannot be reliably determined. Furthermore, variability associated with adverse reaction reporting, the terminology used to describe adverse reactions, etc., limit the value of the quantitative frequency estimates provided. Reaction frequencies are calculated as the number of patients who used ZOMIG nasal spray and reported a reaction divided by the total number of patients exposed to ZOMIG nasal spray (n=3059). All reported reactions are included except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug. Reactions are further classified within body system categories and enumerated in order of decreasing frequency using the

following definitions: infrequent adverse reactions are those occurring in 1/100 to 1/1,000 patients and rare adverse reactions are those occurring in fewer than 1/1,000 patients.

General: Infrequent: allergic reactions.

Cardiovascular: Infrequent: arrhythmias, hypertension, syncope and tachycardia. Rare: angina pectoris and myocardial infarct.

Digestive: Rare: stomatitis.

Neurological: Infrequent: agitation, amnesia, anxiety, depression, insomnia, and nervousness. Rare: convulsions.

Respiratory: Infrequent: bronchitis, increased cough, dyspnea, epistaxis, laryngeal edema, pharyngitis, rhinitis, and sinusitis.

Skin: Infrequent: pruritus, rash, and urticaria.

Urogenital: Infrequent: polyuria and urinary urgency. Rare: urinary frequency.

Special senses: Infrequent: tinnitus. Rare: conjunctivitis, dry eye, and visual field defect.

The adverse reaction profile seen with ZOMIG nasal spray is similar to that seen with ZOMIG tablets and ZOMIG-ZMT tablets except for the occurrence of local adverse reactions from the nasal spray *(see ZOMIG tablet/ZOMIG-ZMT oral disintegrating tablet Prescribing Information)*.

Pediatric Patients 12 to 17 Years of Age

The safety of ZOMIG nasal spray in the acute treatment of migraine in pediatric patients 12 to 17 years of age was established in two studies *[see Pediatric Use (8.4) and Clinical Studies (14.2)]*.

The most common adverse reactions (incidence of ≥ 2% of pediatric patients receiving 2.5 mg and 5 mg ZOMIG nasal spray and numerically greater than placebo) after a single dose are summarized in Table 2. Dysgeusia (unusual taste) was the most common adverse reaction, with a numerically greater incidence for patients receiving ZOMIG compared to placebo (10% vs. 2%). Other common adverse reactions were nasal discomfort, dizziness, oropharyngeal pain, and nausea.

Table 2 lists the adverse reactions from the pooled placebo-controlled studies that occurred in ≥ 2% of pediatric patients 12 to 17 years of age in either the 2.5 mg or 5 mg ZOMIG dose groups and with an incidence greater than placebo.

Table 2: Adverse reactions in Pooled Placebo-Controlled Studies in Pediatric Patients 12 to 17 years of Age with Migraine

Adverse Reaction	Placebo (N=437)	ZOMIG 2.5 mg (N=81)	ZOMIG 5 mg (N=431)
Unusual taste	2%	6%	10%
Nasal discomfort	1%	3%	3%
Dizziness	1%	0%	2%
Oropharyngeal pain	2%	0%	2%
Nausea	1%	1%	2%

The adverse reaction profile was similar across gender. There were insufficient data to assess the impact of race on the incidence of adverse reactions.

6.2 Postmarketing Experience

The following adverse reactions were identified during post approval use of ZOMIG. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The reactions enumerated include all except those already listed in the Clinical Trials Experience section above or the Warnings and Precautions section.

Hypersensitivity Reactions:

There have been reports of anaphylaxis, anaphylactoid, and hypersensitivity reactions including angioedema in patients receiving ZOMIG. ZOMIG is contraindicated in patients with a history of hypersensitivity reaction to ZOMIG.

7 DRUG INTERACTIONS

7.1 Ergot-containing drugs

Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and ZOMIG within 24 hours of each other is contraindicated [*see Contraindications (4)*].

7.2 MAO-A Inhibitors

MAO-A inhibitors increase the systemic exposure of zolmitriptan. Therefore, the use of ZOMIG in patients receiving MAO-A inhibitors is contraindicated [*see Contraindications (4) and Clinical Pharmacology (12.3)*].

7.3 5-HT$_{1B/1D}$ agonists (e.g. triptans)

Concomitant use of other 5-HT$_{1B/1D}$ agonists (including triptans) within 24 hours of ZOMIG treatment is contraindicated because the risk of vasospastic reactions may be additive [*see Contraindications (4)*].

7.4 Cimetidine

Following administration of cimetidine, the half-life and AUC of ZOMIG and its active metabolites were approximately doubled [*see Clinical Pharmacology (12.3)*]. If cimetidine and ZOMIG are used concomitantly, limit the maximum single dose of ZOMIG to 2.5 mg, not to exceed 5 mg in any 24-hour period [*see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)*].

7.5 Selective Serotonin Reuptake Inhibitors/Serotonin Norepinephrine Reuptake Inhibitors and Serotonin Syndrome

Cases of life-threatening serotonin syndrome have been reported during combined use of selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) and triptans [*see Warnings and Precautions (5.7)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women; therefore, zolmitriptan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In reproductive toxicity studies in rats and rabbits, oral administration of zolmitriptan to pregnant animals resulted in embryolethality and fetal abnormalities (malformations and variations) at clinically relevant exposures.

When zolmitriptan was administered to pregnant rats during the period of organogenesis at oral doses of 100, 400, and 1200 mg/kg/day (plasma exposures (AUCs) ≈280, 1100, and 5000 times the human AUC at the maximum recommended human dose (MRHD) of 10 mg/day), there was a dose-related increase in embryolethality. A no-effect dose for embryolethality was not established. When zolmitriptan was administered to pregnant rabbits during the period of organogenesis at oral doses of 3, 10, and 30 mg/kg/day (plasma AUCs ≈1, 11, and 42 times the human AUC at the MRHD), there were increases in embryolethality and in fetal malformations and variations. The no-effect dose for adverse effects on embryo-fetal development was associated with a plasma AUC similar to that in humans at the MRHD. When female rats were given zolmitriptan during gestation, parturition, and lactation at oral doses of 25, 100, and 400 mg/kg/day (plasma AUCs ≈70, 280, and 1100 times that in human at the MRHD), an increased incidence of hydronephrosis was found in the offspring. The no-effect dose was associated with a plasma AUC ≈280 times that in humans at the MRHD.

8.3 Nursing Mothers

It is not known whether zolmitriptan is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in

nursing infants from ZOMIG, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. In rats, oral dosing with zolmitriptan resulted in levels in milk up to 4 times higher than in plasma.

8.4 Pediatric Use

Safety and effectiveness of ZOMIG in pediatric patients under 12 years of age have not been established.

The efficacy of ZOMIG nasal spray in the acute treatment of migraine in pediatric patients 12 to 17 years of age was established in a placebo-controlled study with a total of 81 pediatric patients receiving ZOMIG 2.5 mg and 229 pediatric patients receiving ZOMIG 5 mg *[see Clinical Studies (14.2)]*.

In an earlier study with a different design, ZOMIG 5 mg nasal spray was evaluated in the acute treatment of migraine headache in 171 pediatric patients 12 to 17 years of age. In that study, the efficacy of ZOMIG nasal spray was not established.

The safety of ZOMIG nasal spray in the acute treatment of migraine in pediatric patients 12 to 17 years of age was established in two placebo-controlled studies with a total of 81 pediatric patients receiving ZOMIG 2.5 mg and 431 pediatric patients receiving ZOMIG 5 mg *[see Adverse Reactions (6.1)]*.

The safety profile of ZOMIG nasal spray in pediatric patients 12 to 17 years of age is similar to the profile observed in adults *[see Adverse Reactions (6.1)]*.

In the postmarketing experience with triptans, including ZOMIG, there is a limited number of reports that describe pediatric patients who have experienced clinically serious adverse events; those that were reported are similar in nature to those reported rarely in adults.

8.5 Geriatric Use

Clinical studies of ZOMIG did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Geriatric patients who have other cardiovascular risk factors (e.g., diabetes, hypertension, smoking, obesity, strong family history of coronary artery disease) should have a cardiovascular evaluation prior to receiving ZOMIG [*see Warnings and Precautions (5.1)*]. The pharmacokinetics of zolmitriptan were similar in geriatric patients (aged > 65 years) compared to younger patients [*see Clinical Pharmacology (12.3)*].

8.6 Hepatic Impairment

The effect of hepatic disease on the pharmacokinetics of zolmitriptan nasal spray has not been evaluated. After oral administration, zolmitriptan blood levels were increased in patients with moderate to severe hepatic impairment, and significant elevation in blood pressure was observed in some of these patients [*see Warnings and Precautions (5.8)*]. ZOMIG nasal spray is not recommended in patients with moderate to severe hepatic impairment [*see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

There is no experience with acute overdose. Clinical study subjects receiving single 50 mg oral doses of zolmitriptan commonly experienced sedation.

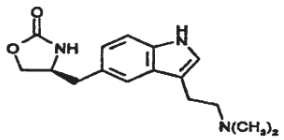
The elimination half-life of ZOMIG is 3 hours [*see Clinical Pharmacology (12.1)*] and therefore monitoring of patients after overdose with ZOMIG should continue for at least 15 hours or while symptoms or signs persist.

There is no specific antidote to zolmitriptan. In cases of severe intoxication, intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system.

It is unknown what effect hemodialysis or peritoneal dialysis has on the plasma concentrations of zolmitriptan.

11 DESCRIPTION

ZOMIG® (zolmitriptan) Nasal Spray contains zolmitriptan, which is a selective 5-hydroxytryptamine $_{1B/1D}$ (5-$HT_{1B/1D}$) receptor agonist. Zolmitriptan is chemically designated as (S)-4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-2-oxazolidinone and has the following chemical structure:



The empirical formula is $C_{16}H_{21}N_3O_2$, representing a molecular weight of 287.36. Zolmitriptan is a white to almost white powder that is readily soluble in water. ZOMIG Nasal Spray is supplied as a clear to pale yellow solution of zolmitriptan, buffered to a pH 5.0. Each ZOMIG Nasal Spray contains 2.5 mg or 5 mg of zolmitriptan in a 100-µL unit dose aqueous buffered solution containing citric acid, anhydrous, USP, disodium phosphate dodecahydrate USP and purified water USP.

ZOMIG Nasal Spray is hypertonic. The osmolarity of ZOMIG Nasal Spray for 2.5 mg is 360 to 420 mOsmol, and for 5 mg is 420 to 470 mOsmol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Zolmitriptan binds with high affinity to human recombinant 5-HT_{1D} and 5-HT_{1B} receptors, and moderate affinity for 5-HT_{1A} receptors. The N-desmethyl metabolite also has high affinity for 5-$HT_{1B/1D}$ and moderate affinity for 5-HT_{1A} receptors.

Current theories proposed to explain the etiology of migraine headache suggest that symptoms are due to local cranial vasodilatation and/or to the release of sensory neuropeptides (vasoactive intestinal peptide, substance P and calcitonin gene-related peptide) through nerve endings in the trigeminal system. The therapeutic activity of ZOMIG for the treatment of migraine headache is thought to be due to the agonist effects at the 5-$HT_{1B/1D}$ receptors on intracranial blood vessels (including the arterio-venous anastomoses) and sensory nerves of the trigeminal system which result in cranial vessel constriction and inhibition of pro-inflammatory neuropeptide release.

12.3 Pharmacokinetics

Absorption

Zolmitriptan nasal spray is rapidly absorbed via the nasopharynx as detected in a Photon Emission Tomography (PET) study using ^{11}C zolmitriptan. The mean relative bioavailability of the nasal spray formulation is 102%, compared with the oral tablet. Zolmitriptan was detected in plasma by 5 minutes and peak plasma concentration generally was achieved by 3 hours. The time at which maximum plasma concentrations were observed was similar after single (1 day) or multiple (4 days) nasal dosing. Plasma concentrations of zolmitriptan are sustained for 4 to 6 hours after dosing. Zolmitriptan and its active N-desmethyl metabolite display linear kinetics after single or multiple doses of ZOMIG nasal spray over the dose range of 0.1 to 10 mg.

The pharmacokinetics of the N-desmethyl metabolite are similar to that of zolmitriptan for all nasal spray dosages. The N-desmethyl metabolite is detected in plasma by 15 minutes and peak plasma concentration is generally achieved by 3 hours after administration.

Food has no significant effect on the bioavailability of zolmitriptan.

Distribution

Plasma protein binding of zolmitriptan is 25% over the concentration range of 10-1000 ng/mL. The mean apparent volume of distribution for zolmitriptan nasal spray formulation is 8.4 L/kg.

Metabolism
Zolmitriptan is converted to an active N-desmethyl metabolite such that the metabolite concentrations are about two-thirds that of zolmitriptan. Because the $5HT_{1B/1D}$ potency of the metabolite is 2 to 6 times that of the parent compound, the metabolite may contribute a substantial portion of the overall effect after ZOMIG administration.

Excretion
The mean elimination half-life for zolmitriptan and N-desmethyl metabolite following single or multiple nasal spray administration are approximately 3 hours, similar to the half-life values seen after oral tablet administration.

In a study with orally administered zolmitriptan, total radioactivity recovered in urine and feces was 65% and 30% of the administered dose, respectively. In urine, unchanged zolmitriptan and N-desmethyl metabolite accounted for 8% and 4% of the dose, respectively, whereas the inactive indole acetic acid and N-oxide metabolites accounted for 31% and 7% of the dose, respectively.

Mean total plasma clearance for zolmitriptan nasal spray is 25.9 mL/min/kg, of which one-sixth is renal clearance. The renal clearance is greater than the glomerular filtration rate suggesting renal tubular secretion.

Specific Populations

Age:
The pharmacokinetics of orally administered zolmitriptan in healthy elderly non-migraineur volunteers (age 65-76 yrs) was similar to those in younger non-migraineur volunteers (age 18-39 yrs).

Sex:
Mean plasma concentrations of orally administered zolmitriptan were up to 1.5-fold higher in females than males.

Race:
There are no significant differences in the pharmacokinetics of orally administered zolmitriptan in Japanese and Caucasians.

Renal Impairment:
The effect of renal impairment on the pharmacokinetics of zolmitriptan nasal spray has not been evaluated. After orally dosing zolmitriptan, renal clearance was reduced by 25% in patients with severe renal impairment (Clcr $\geq 5 \leq 25$ mL/min) compared with the normal group (Clcr ≥ 70 mL/min); no significant change in clearance was observed in the moderately renally impaired group (Clcr $\geq 26 \leq 50$ mL/min).

Hepatic Impairment:
The effect of hepatic disease on the pharmacokinetics of zolmitriptan nasal spray has not been evaluated. In patients with severe hepatic impairment, the mean C_{max}, T_{max}, and

AUC of zolmitriptan dosed orally were increased 1.5-fold, 2-fold (2 vs. 4 hours), and 3-fold, respectively, compared to subjects with normal hepatic function. Seven out of 27 patients experienced 20 to 80 mm Hg elevations in systolic and/or diastolic blood pressure after a 10 mg ZOMIG dose [*see Dosage and Administration (2.2) and Use in Specific Populations (8.6)*].

Hypertensive Patients:
No differences in the pharmacokinetics of oral zolmitriptan or its effects on blood pressure were seen in mild to moderate hypertensive volunteers compared with normotensive controls.

Drug Interactions
All drug interaction studies were performed in healthy volunteers using a single 10 mg dose of zolmitriptan and a single dose of the other drug except where otherwise noted. Eight drug interaction studies have been performed with zolmitriptan tablets and one study (xylometazoline) was performed with nasal spray.

Xylometazoline:
An *in vivo* drug interaction study with ZOMIG nasal spray indicated that 1 spray (100 µL dose) of xylometazoline (0.1% w/v), a decongestant, administered 30 minutes prior to a 5 mg nasal dose of zolmitriptan did not alter the pharmacokinetics of zolmitriptan.

Fluoxetine:
The pharmacokinetics of zolmitriptan, as well as its effect on blood pressure, were unaffected by 4 weeks of pre-treatment with oral fluoxetine (20 mg/day).

MAO Inhibitors:
Following one week of administration of moclobemide (150 mg twice-daily), a specific MAO-A inhibitor, there was an increase of about 25% in both C_{max} and AUC for zolmitriptan and a 3-fold increase in the C_{max} and AUC of the active N-desmethyl metabolite of zolmitriptan [*see Contraindications (4) and Drug Interactions (7.2)*].

Selegiline, a selective MAO-B inhibitor, at a dose of 10 mg/day for 1 week, had no effect on the pharmacokinetics of zolmitriptan and its metabolite.

Propranolol:
C_{max} and AUC of zolmitriptan increased 1.5-fold after one week of dosing with propranolol (160 mg/day). C_{max} and AUC of the N-desmethyl metabolite were reduced by 30% and 15%, respectively. There were no interactive effects on blood pressure or pulse rate following administration of propranolol with zolmitriptan.

Acetaminophen:
A single 1g dose of acetaminophen does not alter the pharmacokinetics of zolmitriptan and its N-desmethyl metabolite. However, zolmitriptan delayed the T_{max} of acetaminophen by one hour.

Metoclopramide:
A single 10 mg dose of metoclopramide had no effect on the pharmacokinetics of zolmitriptan or its metabolites.

Oral Contraceptives:
Retrospective analysis of pharmacokinetic data across studies indicated that mean C_{max} and AUC of zolmitriptan were 30% and 50% higher, respectively, and T_{max} was delayed by one-half hour in females taking oral contraceptives compared to females not taking oral contraceptives. The effect of zolmitriptan on the pharmacokinetics of oral contraceptives has not been studied.

Cimetidine:
Following the administration of cimetidine, the half-life and AUC of a 5 mg dose of zolmitriptan and its active metabolite were approximately doubled. A dosage adjustment is therefore required [*see Drug Interactions (7.4)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Zolmitriptan was administered to mice and rats at doses up to 400 mg/kg/day. Mice were dosed for 85 weeks (males) and 92 weeks (females); rats were dosed for 101 weeks (males) and 86 weeks (females). There was no evidence of drug-induced tumors in mice at plasma exposures (AUC) up to approximately 700 times that in humans at the maximum recommended human dose (MRHD) of 10 mg/day. In rats, there was an increase in the incidence of thyroid follicular cell hyperplasia and thyroid follicular cell adenomas in male rats receiving 400 mg/kg/day. No increase in tumors was observed in rats at 100 mg/kg/day, a dose associated with a plasma AUC ≈700 times that in humans at the MRHD.

Mutagenesis
Zolmitriptan was positive in an *in vitro* bacterial reverse mutation (Ames) assay and in an *in vitro* chromosomal aberration assay in human lymphocytes. Zolmitriptan was negative in an *in vitro* mammalian gene cell mutation (CHO/HGPRT) assay and in oral *in vivo* micronucleus assays in mouse and rat.

Impairment of Fertility
Studies of male and female rats administered zolmitriptan prior to and during mating and up to implantation showed no impairment of fertility at oral doses up to 400 mg/kg/day. The plasma exposure (AUC) at this dose was approximately 3000 times that in humans at the MRHD.

14 CLINICAL STUDIES

14.1 Adults

The efficacy of ZOMIG nasal spray 2.5 mg and 5 mg in the acute treatment of migraine headache with or without aura in adults was demonstrated in Study 1, a randomized, outpatient, double-blind, placebo-controlled trial.

In Study 1, patients were instructed to treat a moderate to severe headache. Headache response, defined as a reduction in headache severity from moderate or severe pain to mild or no pain, was assessed 15, 30, 45 minutes and 1, 2, and 4 hours after dosing. Pain-free response rates and associated symptoms such as nausea, photophobia, and phonophobia were also assessed. A dose of escape medication was allowed 4 to 24 hours after the initial treatment for persistent and recurrent headache.

In Study 1, of the patients taking ZOMIG nasal spray 2.5 mg or 5 mg, 83% were female and 99% were Caucasian, with a mean age of 41 years (range 18 to 65 years).

The two-hour headache response rates in patients treated with ZOMIG nasal spray were significantly higher among patients receiving ZOMIG nasal spray at all doses, compared with placebo (see Table 3).

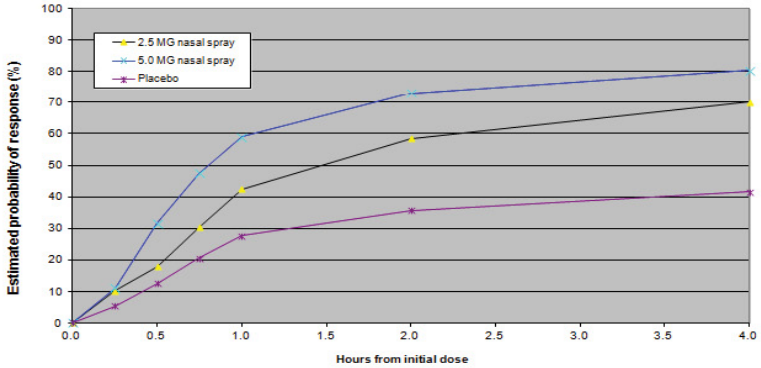
Table 3: First Attack Data: Percentage of Adult Patients with Headache Response to ZOMIG Nasal Spray (Mild or No Headache) 2 Hours Following Treatment in Study 1

PLACEBO (N=218)	ZOMIG 2.5 mg (N=219)	ZOMIG 5 mg (N=228)
31%	55%*	69%*

*p < 0.001 in comparison with placebo

The estimated probability of achieving an initial headache response following treatment with ZOMIG nasal spray is depicted in Figure 1.

Figure 1: Estimated probability of achieving an initial headache response after treatment in Study 1

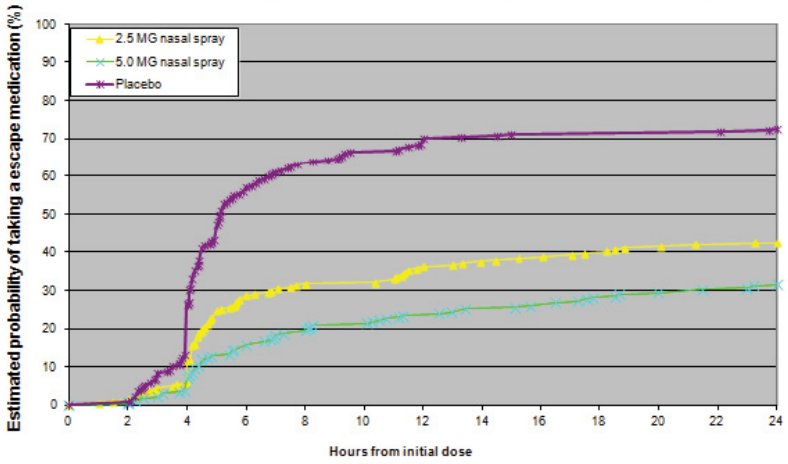


Note: Figure 1 shows the Kaplan-Meier plot of the probability over time of obtaining headache response (moderate or severe headache improving to mild or no pain) following treatment with ZOMIG nasal spray. The estimates displayed are based on a placebo controlled, outpatient trial providing evidence of efficacy. Patients not achieving headache response or taking additional treatment prior to 4 hours were censored to 4 hours.

For patients with migraine associated photophobia, phonophobia, and nausea at baseline, there was a decreased incidence of these symptoms following administration of ZOMIG nasal spray as compared with placebo.

Four to 24 hours following the initial dose of study treatment, patients were allowed to use additional treatment for pain relief in the form of a second dose of study treatment or other medication. The estimated probability of patients taking a second dose or other medication for migraine over the 24 hours following the initial dose of study treatment is summarized in Figure 2.

Figure 2: Estimated probability of patients taking an escape medication within the 24 hours following the initial dose of study treatment in Study 1



*This Kaplan-Meier plot is based on data obtained from the placebo controlled clinical trial. Patients not using additional treatments were censored at 24 hours. The plot includes both patients who had headache response at 2 hours and those who had no response to the initial dose. It should be noted that the protocol did not allow remedication within 4 hours post dose.

The efficacy of ZOMIG was unaffected by presence of aura; presence of headache upon awakening, relationship to menses; gender, age or weight of the patient; or presence of pre-treatment nausea.

The efficacy of ZOMIG nasal spray 5 mg was further supported by an interim analysis of another similarly designed trial. The 2-hour headache response rates for the first 210 subjects in that study for ZOMIG 5 mg and placebo were 70% and 47%, respectively (N=108 and 102, respectively, p=0.0006).

14.2 Pediatric Patients 12 to 17 Years of Age

The efficacy of ZOMIG nasal spray in the acute treatment of migraine headache with or without aura in pediatrics patients 12 to 17 years of age was demonstrated in Study 2, a randomized, double-blind, placebo-controlled trial with a single-blind run-in period.

Patients had to have an established diagnosis of migraine (history indicating the presence of migraine for at least 1 year) with or without aura with a typical untreated migraine headache attack lasting 3 hours or more. The study included treatment of a single migraine headache attack with 1 dose of single-blind placebo during the 30-day run-in period. If the patient met all conditions for randomization, including a lack of response to the placebo run-in, a subsequent single migraine headache attack was treated with 1 blinded dose of either ZOMIG nasal spray 5 mg, 2.5 mg, or matching placebo.

In Study 2, of the patients taking ZOMIG nasal spray 2.5 mg or 5 mg, 62% were female and 93% were Caucasian, with a mean age of 14 years (range 12 to 17 years).

Study 2 evaluated the proportion of pediatric patients 12 to 17 years of age who had no headache pain at 2 hours following treatment. Headache response (defined as a reduction in migraine-related headache pain severity from moderate orsevere pain to mild or no pain) and the absence of nausea, photophobia, and phonophobia at 2 hours post treatment were also assessed. As shown in Table 4, the percentage of pediatric patients 12 to 17 years of age with no headache pain at 2 hours following treatment was significantly higher for ZOMIG nasal spray 5 mg than placebo.

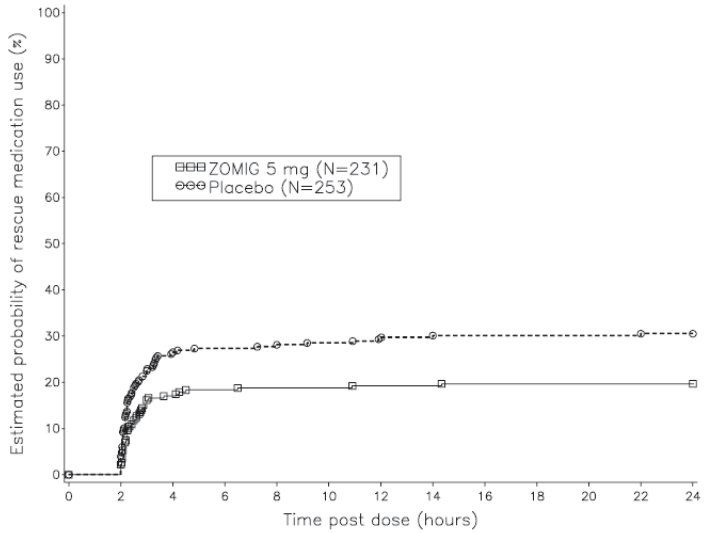
Table 4: Percentage of Pediatric Patients 12 to 17 Years of Age with No Headache Pain, With Headache Response, No Nausea, No Photophobia, and No Phonophobia Two Hours after Treatment in Study 2

Two Hours Following Treatment			
	Placebo (N=253)	ZOMIG 2.5 mg (N=81)	ZOMIG 5 mg (N=229)
No Headache Pain	17%	25%	30%*
With Headache Response	39%	53%*	51%*
No Photophobia	44%	66%*	56%*
No Phonophobia	48%	61%*	58%*
No Nausea	66%	70%	72%

*$p < 0.05$ in comparison with placebo

Two to 24 hours following the initial dose of study treatment, patients were allowed to use their usual medication for pain relief. The estimated probability of patients taking escape medication during the first 24 hours following the initial dose of study treatment is summarized in Figure 3.

Figure 3: Estimated Probability of Pediatric Patients 12 to 17 Years of Age Taking an Escape Medication Within the 24 Hours Following the Initial Dose of Study Treatment in Study 2



16 HOW SUPPLIED/STORAGE AND HANDLING

The ZOMIG Nasal Spray device is a blue-colored plastic device with a gray protection cap, labeled to indicate the nominal dose. Each ZOMIG Nasal Spray device administers a single dose of ZOMIG.

ZOMIG Nasal Spray is supplied as a clear to pale yellow solution of zolmitriptan, buffered to a pH 5.0. Each ZOMIG Nasal Spray device contains 2.5 mg or 5 mg of zolmitriptan in a 100 µL unit dose aqueous buffered solution containing citric acid, anhydrous, USP, disodium phosphate dodecahydrate USP and purified water USP.

2.5 mg ZOMIG® Nasal Spray is supplied in boxes of 6 single-use nasal spray units. (NDC 64896-682-51)

5 mg ZOMIG® Nasal Spray is supplied in boxes of 6 single-use nasal spray units. (NDC 64896-681-51).

Each ZOMIG® Nasal Spray single dose unit spray supplies 2.5 and 5 mg, respectively, of zolmitriptan. The ZOMIG® Nasal Spray unit must be discarded after use.

Store at controlled room temperature, 20-25°C (68-77°F) [see USP].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Risk of Myocardial Ischemia and/or Infarction, Prinzmetal's angina, Other Vasospasm-related Events, and Cerebrovascular Events
Inform patients that ZOMIG may cause serious cardiovascular side effects such as myocardial infarction or stroke, which may result in hospitalization and even death. Although serious cardiovascular events can occur without warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for medical advice when observing any indicative sign or symptoms [*see Warnings and Precautions (5.1, 5.2, 5.4, 5.5)*].

Medication Overuse Headache
Inform patients that use of acute migraine drugs for 10 or more days per month may lead to an exacerbation of headache, and encourage patients to record headache frequency and drug use (e.g., by keeping a headache diary) [*see Warnings and Precautions (5.6)*].

Serotonin Syndrome
Inform patients about the risk of serotonin syndrome with the use of ZOMIG or other triptans, particularly during combined use with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) [see *Warnings and Precautions (5.7)*].

Pregnancy
Inform patients that ZOMIG should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus [*see Use in Specific Populations (8.1)*].

Nursing Mothers
Advise patients to notify their healthcare provider if they are breastfeeding or plan to breastfeed [*see Use in Specific Populations (8.3)*].

Handling of ZOMIG nasal spray device
The ZOMIG Nasal Spray device is packaged in a carton and is a blue-colored plastic device with a gray protection cap, labeled to indicate the nominal dose. Caution patients to not remove the gray protection cap until prior to dosing. The ZOMIG Nasal Spray device is placed in a nostril and actuated to deliver a single dose. Caution patients to avoid spraying the contents of the device in their eyes.

Patient Information

ZOMIG® (Zo-mig)
(zolmitriptan)
Nasal Spray

Please read this information before you start taking ZOMIG Nasal Spray and each time you renew your prescription just in case anything has changed. Remember, this summary does not take the place of discussions with your doctor. You and your doctor should discuss ZOMIG Nasal Spray when you start taking your medication and at regular checkups.

What is ZOMIG Nasal Spray?

ZOMIG Nasal Spray is a prescription medicine used to treat migraine headaches with or without aura in adults andpediatric patients (12 to 17 years of age).

ZOMIG Nasal Spray is not for other types of headaches.

ZOMIG Nasal Spray is not for the prevention of migraine headaches.

It is not known if ZOMIG Nasal Spray is safe and effective to treat cluster headaches.

ZOMIG Nasal Spray is not for people with moderate or severe liver problems (hepatic impairment).

It is not known if ZOMIG Nasal Spray is safe and effective in children under 12 years of age.

Who should not use ZOMIG Nasal Spray?

Do not use ZOMIG Nasal Spray if you have:

- heart problems, a history of heart problems, or problems with the electrical system of your heart
- had a stroke, transient ischemic attacks (TIAs), or problems with your blood circulation
- hemiplegic migraines or basilar migraines. If you are not sure if you have these types of migraines, ask your healthcare provider.
- narrowing of blood vessels to your legs, arms, or stomach (peripheral vascular disease)
- uncontrolled high blood pressure
- used certain medicines called 5-HT_1 agonists ("triptans") such as almotriptan (AXERT®), eletriptan (RELPAX®), frovatriptan (FROVA®), naratriptan (AMERGE®), rizatriptan (MAXALT®), sumatriptan (IMITREX®), sumatriptan/naproxen (TREXIMET®); medicines that contain ergotamine, or ergot medicines such as BELLERGAL-S®, CAFERGOT®, ERGOMAR®, WIGRAINE®; dihydroergotamine like D.H.E. 45® or MIGRANAL®; or methysergide (SANSERT®) in the last 24 hours. Ask your doctor or pharmacist for a list of these medicines if you are not sure.
- are taking a monoamine oxidase A inhibitor (MAO-A inhibitor) or you stopped taking a MAO-A inhibitor in the last 14 days. Ask your doctor if you are not sure if you take an MAO-A inhibitor such as phenelzine sulfate (NARDIL®) or tranylcypromine sulfate (PARNATE®).
- are allergic to zolmitriptan or any of the ingredients in ZOMIG Nasal Spray.
  See the end of this leaflet for a complete list of ingredients in ZOMIG Nasal Spray.

What should I tell my doctor before using ZOMIG Nasal Spray?

Before using ZOMIG Nasal Spray, tell your doctor about all of your medical conditions, including if you:

- have high blood pressure
- have high cholesterol
- have diabetes
- smoke
- are overweight
- are a female who has gone through menopause
- have heart disease or a family history of heart disease or stroke
- have liver problems
- are pregnant or plan to become pregnant. It is not known if ZOMIG Nasal Spray will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if ZOMIG Nasal Spray passes into your breast milk. You and your doctor should decide if you will use ZOMIG Nasal Spray or breastfeed.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Especially tell your doctor if you take:

- medicines used to treat mood disorders, including selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs) or monoamine oxidase inhibitors (MAOIs).
- cimetidine

How should I use ZOMIG NASAL Spray?

For detailed instructions, see the step-by-step instructions for using ZOMIG Nasal Spray at the end of this Patient Information.

- Certain people should take their first dose of ZOMIG Nasal Spray in their doctor's office or in another medical setting. Ask your doctor if you should take your first dose in a medical setting.
- Use ZOMIG Nasal Spray exactly as your doctor tells you to use it.
- Your doctor may change your dose. Do not change your dose without first talking with your doctor.
- If your headache comes back after using one nasal spray or you only get some relief from your headache, you can use another nasal spray 2 hours after the previous nasal spray.
- **Do not** use more than a total of 10 mg of ZOMIG Nasal Spray in any 24-hour period.
- It is not known if it is safe and effective to use ZOMIG Nasal Spray for more than 4 headaches in 30 days.
- Some people who use too much ZOMIG Nasal Spray may have worse headaches (medication overuse headaches). If your headaches get worse, your doctor may decide to stop your treatment with ZOMIG Nasal Spray.
- If you use too much ZOMIG Nasal Spray, call your doctor or go to the nearest hospital emergency room right away.
- You should write down when you have headaches and when you take ZOMIG Nasal Spray so you can talk to your doctor about how ZOMIG Nasal Spray is working for you.

What should I avoid while using ZOMIG Nasal Spray?
ZOMIG Nasal Spray can cause dizziness, weakness, or drowsiness. If you have these symptoms do not drive a car, use machinery, or do anything that needs you to be alert.

What are the possible side effects of ZOMIG Nasal Spray?

ZOMIG Nasal Spray can cause serious side effects.

Call your doctor right away if you have any of the following symptoms after using ZOMIG Nasal Spray:

- **Heart attack and other heart problems.** Heart problems may lead to death. Stop taking ZOMIG Nasal Spray and get emergency medical help right away if you have any of the following symptoms of a heart attack or other heart problems:
  - discomfort in the center of your chest that lasts for more than a few minutes, or that goes away and comes back
  - chest pain or chest discomfort that feels like heavy pressure, squeezing, or fullness
  - pain or discomfort in your arms, back, neck, jaw, or stomach
  - shortness of breath with or without chest discomfort
  - breaking out in a cold sweat
  - feeling lightheaded
  - nausea or vomiting with any of the symptoms included above
- **stroke.** Symptoms of stroke include face drooping, slurred speech, and unusual weakness or numbness.
- **changes in color or sensation in your fingers and toes (Raynaud's syndrome)**
- **stomach and intestinal problems** (gastrointestinal and colonic ischemic events). Symptoms of gastrointestinal and colonic ischemic events include:
  - sudden or severe stomach pain
  - stomach pain after meals
  - weight loss
  - nausea or vomiting
  - constipation or diarrhea
  - bloody diarrhea
  - fever
- **problems with blood circulation to your legs and feet** (peripheral vascular ischemia). Symptoms of peripheral vascular ischemia include:
  - cramping and pain in your legs or hips
  - feeling of heaviness or tightness in your leg muscles
  - burning or aching pain in your feet or toes while resting
  - numbness, tingling, or weakness in your legs
  - cold feeling or color changes in 1 or both legs or feet
- **serotonin syndrome.** Serotonin syndrome is a serious and life-threatening problem that can happen in people using ZOMIG Nasal Spray, especially if ZOMIG Nasal Spray is used with anti-depressant

medicines called selective serotonin reuptake inhibitors (SSRIs) or selective norephinephrine reuptake inhibitors (SNRIs).

Ask your doctor or pharmacist for a list of these medicines if you are not sure.

Call your doctor right away if you have any of the following symptoms of serotonin syndrome:

- mental changes such as seeing things that are not there (hallucinations), agitation, or coma
- fast heartbeat
- changes in blood pressure
- high body temperature
- tight muscles
- trouble walking
- nausea, vomiting, or diarrhea

- **increased blood pressure**
- **allergic reactions.** Symptoms of an allergic reaction include:
  - rash
  - hives
  - itching
  - swelling of the face, mouth throat, or tongue
  - difficulty breathing

The most common side effects of ZOMIG Nasal Spray are:

- unusual taste
- numbness
- dizziness
- skin sensitivity (hyperparesthesia)

These are not all the possible side effects of ZOMIG Nasal Spray. For more information ask your doctor or pharmacist.

Call your doctor for medical advice about side effects.
You may report side effects to FDA at 1-800-FDA-1088.

How should I store ZOMIG Nasal Spray?

Store ZOMIG Nasal Spray at room temperature between 68°F to 77°F (20°C -25°C).

Keep ZOMIG Nasal Spray and all medicines out of the reach of children.

General information about the safe and effective use of ZOMIG Nasal Spray.

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets. Do not use ZOMIG Nasal Spray for a condition for which it was not prescribed. Do not give ZOMIG Nasal Spray to other people, even if they have the same symptoms that you have. It may harm them.

This leaflet summarizes the most important information about ZOMIG Nasal Spray. If you would like more information, talk to your doctor. You can ask your pharmacist or doctor for information about ZOMIG Nasal Spray that is written for health professionals.

For more information go to www.ZOMIG.com or call 1-877-994-6729.

What are the Ingredients in ZOMIG Nasal Spray?

Active ingredient: zolmitriptan

Inactive ingredients: anhydrous citric acid, dibasic sodium phosphate, and purified water

Reference ID: 3778462

Instructions for Use
ZOMIG® (Zo-mig)
(zolmitriptan)
Nasal Spray

Important: For use in your nose only. Do not spray in your eyes.

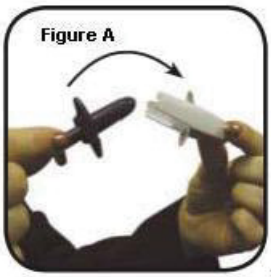
Note: There is only 1 dose in the nasal sprayer. Do not try to prime the nasal sprayer or you will lose the dose. Do not press the plunger until you have put the tip into your nostril or you will lose the dose.

Steps for using ZOMIG Nasal Spray

Step 1. Remove the ZOMIG Nasal Spray unit from the single use package it comes in. Do not remove the unit until you are ready to use it. The unit contains only 1 spray.

Step 2. Blow your nose gently to clear your nasal passages before use.

Step 3. Remove the protective cap **(See Figure A).**



Step 4. Keeping your head in an upright position, gently close 1 nostril with your index finger and breathe out gently through your mouth. **(See Figure B)**. Either nostril can be used.

Reference ID: 3778462

Step 5. With your other hand, hold the container with your thumb supporting the container at the bottom, and your index and middle fingers on each side of the nozzle. **(See Figure C).**

Insert the tip of the sprayer device into your open nostril as far as feels comfortable and tilt your head slightly **(See Figure D).**

Do not press the plunger yet.

Step 6. Breathe in gently through your nose and at the same time press the plunger firmly with your thumb to release your dose of ZOMIG Nasal Spray **(See Figure D).**

The plunger may feel stiff and you may hear a click. Keep your head slightly tilted back and remove the tip from your nose. Breathe gently through your mouth for 5 to 10 seconds. You may feel liquid in your nose or the back of your throat. This is normal.

Step 7. Dispose the ZOMIG Nasal Spray device after completing the full dose or as soon as it becomes outdated or no longer needed. Dispose of properly. Keep out of reach of children. Do not reuse.

This Patient Information and Instructions for Use have been approved by the U.S. Food and Drug Administration.

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