Review Article **CODEN: IJPRNK** **ISSN: 2277-8713**
Bonthu Satyanarayana, IJPRBS, 2013; Volume 2(5):22-38 **IJPRBS**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

NOVEL ANTIMIGRANE AGENT – ZOLMITRIPTAN: A REVIEW

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Accepted Date: 03/09/2013; Published Date: 27/10/2013

Abstract: Present survey is conducted on two species of *Cuscuta (C. chinensis* and *C. reflexa)* which are distributed in different parts of Nadia district especially in Kalyani Township. 30 angiospermic host plants have been identified out of which 25 angispermic plants are infected by *C. reflexa* and only 5 plants has been attacked by *C. chinensis*. All angiospermic plants are distributed in 28 genera and 20 families. 2 plants has been identified as pseudo parasite and 2 plants belonging to pteridophytic group are also attacked by *Cuscuta.* Detailed structure and development of haustoria have been studied on 8 angiospermic plants. *Mikania cordata* is identified as primary host plant of *Cuscuta.* Structure of haustorium is variable which is dependent on some factors. Migraine is a chronic neurological disorder characterized by recurrent moderate to severe headaches often in association with a number of autonomic nervous system symptoms. Typically the headache is unilateral (affecting one half of the head) and pulsating in nature, lasting from 2 to 72 hours. Associated symptoms may include nausea, vomiting, photophobia, phonophobia (increased sensitivity to sound) and the pain is generally aggravated by physical activity. Zolmitriptan is a selective serotonin receptor agonist of the 1B and 1D subtype. It is a triptan, used in the acute treatment of migraine attacks with or without aura and cluster headaches. The efficacy of zolmitriptan appears to be maintained, with no tachyphylaxis, following repeated administration for multiple attacks of migraine over a prolonged period of time, with high headache response rates reported over all attacks.

Keywords: Migrane, Zolmitriptan, Side Effects, Drug & Disease Interactions.

PAPER-QR CODE

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Access Online On:

www.ijprbs.com

How to Cite This Article:

Bonthu Satyanarayana, IJPRBS, 2013; Volume 2(5):22-38

INTRODUCTION

Migraine is a recurrent incapacitating neurovascular disorder characterised by attacks of debilitating pain associated with photophobia, phonophobia, nausea and vomiting. Neurogenic theory considers migraine to be a spreading depression of cortical, electrical activity followed by vascular phenomenon. Migraine is a common and debilitating condition affecting 10-15% of people, migraine attack consists of an initial visual disturbance (the *aura*), in which a flickering pattern, followed by a blind spot progresses gradually across an area of the visual field. This visual disturbance is followed, about 30 minutes later, by a severe throbbing headache, starting unilaterally, often accompanied by photophobia, nausea, vomiting and prostration, which lasts for several hours. In fact, the visual aura occurs only in about 20% of migraine sufferers, although many experience other kinds of premonitory sensation. Sometimes attacks are precipitated by particular foods or by visual stimuli, but more often they occur without obvious cause.[1, 2]

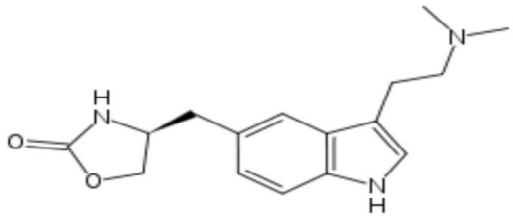
Attacks of migraine typically last from several hours to 2 to 3 days, and many patients suffer one or more attacks a month.[3] Against this background the triptans, selective serotonin 5-HT (1B/1D) agonist are very effective acute migraine drugs with a well developed scientific rationale.

Zolmitriptan is a second generation triptan developed to provide improved pharmacokinetic and optimised trigeminovascular targeting of both the peripheral and central trigeminal terminals[4]. Zolmitriptan (s) – 4 – [3-[2-(dimethylamino) ethyl] – 1H – indol – 5 – yl] methyl] – 2 – oxazolidinone (Fig1). Zolmitriptan contains NLT 98.0% and NMT 102.0% of $C_{16}H_{21}N_3O_2$, calculated on the dried basis.[5] Clinical research indicates that it has a better efficacy and tolerability profile at low doses of 2.5 – 10mg.As a result, zolmitriptan's key attributes include a relatively high oral bioavailability, significant lipophilicity, and the generation of an active hepatic metabolite, 183C91.The pharmacokinetics, efficacy, and tolerability profile of zolmitriptan have been extensively studied using various doses, routes of administration and populations. The results have, demonstrated a similar pharmacokinetic and efficacy profile in subjects.

This review deals with the description and study of zolmitriptan, synthesis, formulations and analytical work done as employed in the treatment of acute migraine.

DRUG INFORMATION:[6]

Structure:



Molecular formula: $C_{16}H_{21}N_3O_2$

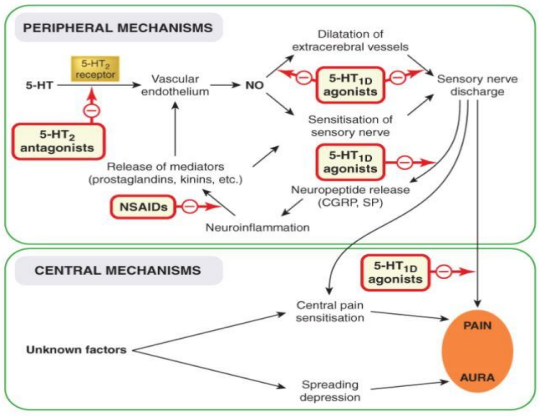
Molecular weight: 287.36

IUPAC Name: (*S*)-4-({3-[2-(dimethylamino)ethyl1*H*-indol-5-yl}methyl)-1,3-oxazolidin-2-one

MECHANISM OF ACTION:[7]

Zolmitroiptan binds with high affinity to human recombinant 5HT 1D & 5HT 1B receptors, and moderate affinity for 5HT 1A receptors. The N-desmethyl metabolite also has high affinity for 5HT 1B/1D and moderate affinity for 5HT 1A receptors.

Migraines are likely due to local cranial vasodialation and/or to the release of sensory neuropeptides through nerve endings in the trigeminal system. The therapeutic activity of zolmitriptan for the treatment of migrane headache is thaught to be due to the agonist effects at the 5HT 1B/1D receptors on intracranial blood vessels and sensory nerves of the trigeminal system which result in cranial vessel constriction and inhibition of pro-inflammatory neuropeptide release.



PREPARATION METHOD:[8]

(S)-4-(4-Aminobenzyl)-l,3-oxazolidine-2-one**(1)** (80 g, 0.4166 moles) was charged to a cooled solution of water (480 mL) and concentrated hydrochloric acid (500 mL) at 5°C to 0°C. To this a solution of sodium nitrite (31.8 g, 0.4614 moles) dissolved in DM water (160 mL) was slowly added at -5 to 0°C. The reaction mass was maintained for 1 hr at -5 to 0°C. The above cold diazonium solution was added at -15 to -10°C, to a pre-cooled solution of stannous chloride (383.76 g, 1.7006 moles) in conc. hydrochloric acid (480 mL). The temperature of the reaction mass was slowly raised to room temperature and maintained for 4 hrs at 25-30°C.

Then to this reaction mass was added DM water (1600 mL), cooled and pH of the reaction mass was adjusted to 1.7-1.85 with 50% sodium hydroxide solution. After pH adjustment, temperature was raised to 25-30°C. If the pH of the reaction mass retains 1.7-1.85, (if not re-adjust to 1.7-1.85), then heat to 96 -103°C maintained for 30 minutes, then added slowly (N,N-dimethyl)

aminobutyraldehyde diethyl acetal (4) (117.92 g, 0.7313 mole) to the reaction mass and maintained for 3-4 hrs at 96 - 103°C.The progress of the reaction was monitored by TLC till the disappearance of hydrazine was observed. The reaction mixture was cooled to 25-30°C, then filtered through high flow bed, collect the stannous chloride cake into fresh round bottom flask add 800 ml of DM water heat the cake to 70-75°C maintain for one hour at 70-75°C, filter through high flow bed subsequently washed with 80 ml hot DM water.

Combined all the filtrate, adjust the pH to 6.9 - 7.0 with sodium hydroxide solution a trace solids were appeared, filtered through high flow bed. The filtrate collected was washed twice with dichloromethane (2X400 ml) to the filtrate, adjusted pH to 10.5 - 11.0 with sodium hydroxide solution extracted with Ethyl acetate (2000ml), organic layer separated, the aqueous layer again extracted with ethyl acetate (400 ml) and the total organic layers were combined, washed with saturated aqueous sodium chloride solution, organic layer concentrated under reduced pressure below 40°C. To get residue, to that residue add isopropyl alcohol (160 ml), heated to 70-75°C maintain for one hour, then cooled to 25-30°C.

To this n-heptane (104 mL) was added at 25-35°C and maintained for 90 minutes. The crystals precipitated was filtered under nitrogen atmosphere and washed with a mixture of Isopropyl alcohol & n-heptane (1:1) (160 ml).

The wet material was suck dried for 10 minutes under nitrogen atmosphere and dried under reduced pressure at 45-50°C for 24 hrs. To the dried material were added 800 mL of DM water into a round bottom flask and stirred for one hour. The slurry thus obtained was filtered and washed with 160 ml DM water and suck dried for 10 minutes under nitrogen atmosphere. The wet material was dissolved in 400 mlisopropyl alcohol at 50°C, charcoalised and filtered mass through Hyflowbed followed by washingwith 160 ml Isopropyl alcohol to the Hyflow bed. The filtrate was concentrated under reducedpressure to 180 ml and cooled to 25-30°C. Then n-heptane 104 ml was added maintain for 60-90 minutes at 15-20°C, filtered under nitrogen atmosphere and washed with mixture of Isopropylalcohol& n-heptane (1:1) (200 ml). The wet material suck dried for 10 minutes under nitrogen atmosphere and dried under reduced pressure at 45-50°C for 10 hrs. Dry weight of product obtained is 56-70g.

PHARMACOKINETICS:[9]

1) **ABSORPTION:** Zolmitriptan is well absorbed after oral administration. It shows a linear kinetics over the dose range of 2.5 to 50mg. the AUC and C_{max} are similar for both ZOMIG tablets and ZOMIG-ZMT orally disintegrating tablets, but the T_{max} is somewhat later with ZOMIG-ZMT.

T_{max} for ZOMIG tablets-1.5 hrs

T_{max} for ZOMIG-ZMT-3hrs

The rate and extent of absorption are not affected by administration with food. Bioavailability is moderate (40%).

2) **DISTRIBUTION:** The mean volume of distribution is 7.0L/Kg. plasma protein binding of zolmitriptan is 25% over the concentration range of 100-1000ng/ml.

3) **METABOLISM:** Hepatic; three metabolites have been identified: indole acetic acid, N-oxide, and N-desmethyl metabolites. However, N-desmethyl is the only active metabolite; the metabolites concentration is two-thirds that of zolmitriptan. Because the 5HT 1B/1D potency of the metabolite is 2-6 times that of the parent compound, the metabolite may contribute a substantial portion of the overall effect after zolmitriptanadministration.

4) **ELIMINATION:** Renal-65% (8% of the dose as unchanged zolmitriptan; 31% as the indole acetic acid metabolite; 7% as the N-oxide metabolite; 4% as the N-desmethyl metabolite Fecal-30%.

5) **HALF-LIFE:** Zolmitriptan: Approximately 3 hours, N-desmethyl metabolite: Approximately 3 hours.

6) **TIME TO PEAK CONCENTRATION:** Tablet-1.5 hours, Orally disintegrating tablet-3 hours.

7) **PROTEIN BINDING:** Low (25%).

PHARMACODYNAMICS:[10] Zolmitriptan is a selective agonist of serotonin (5-hydroxytryptamine; 5-HT) type 1B and 1D receptors. It is structurally and pharmacologically related to other selective 5-HT1B/1D receptor agonists, and has only a weak affinity for 5-HT1A, 5-HT5A, and 5-HT7 receptors and no significant affinity or pharmacological activity at 5-HT2, 5-HT3 or 5-HT4 receptor subtypes or at alpha1-, alpha2-, or beta-adrenergic, dopamine1,; dopamine2; muscarinic, or benzodiazepine receptors. This action in humans correlates with the relief of migraine headache. In addition to causing vasoconstriction, experimental data from animal studies show that Zolmitriptan also activates 5-HT1 receptors on peripheral terminals of the trigeminal nerve innervating cranial blood vessels, which may also contribute to the antimigrainous effect of Zolmitriptan in humans.

INDICATIONS:[11] Zolmitriptan is used for the acute treatment of migraines with or without aura in adults. Zolmitriptan is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine. Zolmitriptan is available as a swallowable tablet, an oral disintegrating tablet, and a nasal spray, in doses of 2.5 and 5 mg. People who get migraines from aspartame should not use the disintegrating tablet (Zomig ZMT), which contains aspartame.

CONTRAINDICATIONS AND PRECAUTIONS:[12] Zolmitriptan should not

be given to patients with ischemic heart disease (angina pectoris, history of myocardial infarction, or documented silent ischemia) or to patients who have symptoms or findings consistent with ischemic heart disease, coronary artery vasospasm, including Prinzmetal's angina, or other significant underlying cardiovascular disease. Zolmitriptan may increase blood pressure, it should not be given to patients with uncontrolled hypertension, should not be used within 24 hours of treatment with another 5-HT1 agonist, or an ergotamine-containing or ergot-type medication like dihydroergotamine or methysergide, and should not be administered to patients with hemiplegic or basilar migraine. Concurrent administration of MAO-A or use of zolmitriptan within 2 weeks of discontinuation of MAO-A inhibitor therapy is contraindicated.

SIDE EFFECTS:[13]

Less serious side effects of zolmitriptan may include:

Pressure or heavy feeling in any part of your body;

Dry mouth, upset stomach;

Severe side effects:

Difficulty in breathing; swelling of face, lips, tongue, or throat.

Use of Zolmitriptan should be stopped if the following serious side effects are seen:

- Feeling of pain or tightness in your jaw, neck, or throat;
- Chest pain or heavy feeling, pain spreading to the arm or shoulder, nausea, sweating, general ill feeling;
- Sudden numbness or weakness, especially on one side of the body;
- Sudden severe headache, confusion, problems with vision, speech, or balance;
- Fast or pounding heartbeats, dizziness;
- Sudden and severe stomach pain and bloody diarrhea;
- Numbness or tingling and a pale or blue-colored appearance in your fingers or toes.
- Agitation, hallucinations, fever, fast heart rate, overactive reflexes, nausea, vomiting, diarrhea, loss of coordination, fainting.
- Feeling of pain or pressure in your neck or throat;
- Drowsiness, weakness; or
- Warmth, redness, or mild tingling under your skin.

Cardiovascular

Cardiovascular side effects including acute myocardial infarction, arrhythmias, hypertension, and syncope have been reported infrequently. Bradycardia,

extrasystoles, postural hypotension, QT prolongation, tachycardia, and thrombophlebitis have rarely been reported.

Most of the serious cardiac events which have been reported occurred in patients with risk factors predicative of coronary artery disease. In a study of patients with liver dysfunction, 7 out of 27 patients experienced 20 to 80 mm Hg elevations in systolic and/or diastolic blood pressure after a 10 mg dose of zolmitriptan.

Nervous system

Nervous system side effects (11% to 21%) including dizziness (6% to 10%), somnolence (5% to 8%), and vertigo (up to 2%) have been reported. Agitation, anxiety, depression, emotional lability, and insomnia have also been reported infrequently. Akathisia, amnesia, apathy, ataxia, dystonia, euphoria, hallucinations, cerebral ischemia, hyperkinesia, hypotonia, hypertonia, and irritability have been reported rarely. Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events including fatalities have been reported in patients treated with 5-HT1 agonists.

Regarding the cerebrovascular events reported in patients treated with 5-HT1 agonists, in a number of cases the cerebrovascular events may have been the primary event, whose symptoms were mistaken for a migraine.

Others

Other side effects including pain and pressure sensations have been reported (13% to 22%). These sensations have included chest pain/tightness/pressure and/or heaviness (2% to 4%), neck/throat/jaw pain/tightness/pressure (4% to 10%), heaviness other than the chest or neck (1% to 5%), pain from a specified location (2% to 3%), and other pressure/tightness/heaviness (2%). Atypical sensations (12% to 18%) including hypoesthesia (1% to 2%), paresthesia (5% to 9%), and warm/cold sensations (5% to 7%) have been reported. Hyperesthesia has been reported infrequently. Asthenia (3% to 9%), palpitations (up to 2%), myalgia (1% to 2%), myasthenia (up to 2%) and drug-induced headache have also been reported. Otic changes including hyperacusis, ear pain, parosmia, and tinnitus have been reported infrequently.

Gastrointestinal

Gastrointestinal ischemic events may present as bloody diarrhea or abdominal pain. Gastrointestinal side effects (11% to 16%) including dry mouth (3% to 5%), dyspepsia (1% to 3%), dysphagia (up to 2%), and nausea (4% to 9%) have been reported. Increase in appetite, tongue edema, esophagitis, gastroenteritis, liver function abnormality, and thirst have been reported infrequently. Anorexia, constipation, gastritis, hematemesis, pancreatitis, melena, and ulcer have been reported rarely. Gastrointestinal ischemic events including splenic infarction, ischemic colitis,

and gastrointestinal infarction or necrosis have been reported very rarely.

General

General side effects including allergic reactions, chills, facial edema, fever, malaise, and photosensitivity have been reported infrequently. Several adverse effects (mostly mild and transient) are dose related, including paresthesia; sensation of heaviness ortightness in the chest, neck, jaw, and throat; dizziness; somnolence; and possibly asthenia, and nausea.

Hematologic

Hematologic side effects including ecchymosis have been reported infrequently. Cyanosis, thrombocytopenia,eosinophilia, and leukopenia have been reported rarely.

Metabolic

Metabolic side effects including edema have been reported infrequently. Hyperglycemia, and increased alkalinephosphatase have been reported rarely.

Musculoskeletal

Musculoskeletal side effects including back pain, leg cramps, and tenosynovitis have been reported infrequently. Arthritis, tetany, myalgia, and twitching have been reported rarely.

Respiratory

Respiratory side effects including bronchitis, bronchospasm, epistaxis, hiccup, laryngitis, and yawn have been reported infrequently. Apnea and voice alteration have been reported rarely.

Hypersensitivity

Hypersensitivity side effects including anaphylaxis and anaphylactoid reaction have been reported.

Ocular

Ocular side effects including dry eye and eye pain have been reported infrequently. Diplopia and lacrimation havebeen reported rarely.

Genitourinary

Genitourinary side effects including hematuria, cystitis, polyuria, urinary frequency, and urinary urgency have beenreported infrequently. Miscarriage and dysmenorrhea have been reported rarely.

Dermatologic

Dermatologic side effects including sweating (up to 3%) have been reported. Pruritus, rash, and urticaria have beenreported infrequently.

DRUG INTERACTIONS:[14] Studies with healthy volunteers showed that zolmitriptan may have interactions with the following drugs:

Other triptans drugs that inhibit the enzyme monoamine oxidase (MAO Inhibitors)

Propranolol (Inderal)

Oral Contraceptives

Cimetidine (Tagamet) drugs that contain ergot, such as ergotamineselective serotonin reuptake inhibitors (SSRIs such as fluoxetine (Prozac))serotonin-norephinephrine reuptake inhibitors (SNRIs such as venlafaxine SSRIs, SNRIs, and monoamine oxidase inhibitors elevate the levels of serotonin in the brain.

When any of these drugs are combined with zolmitriptan, which activates serotonin receptors, the serotonin system in the brain may become over-stimulated. In rare cases a constellation of symptoms, called the serotonin syndrome, results. Symptoms of the syndrome include hallucinations, restlessness, and loss of coordination. The interaction between propranolol and zolmitriptan (10 mg) was investigated in 12 healthy volunteers.

Treatment with propranolol for seven days before giving a single dose of zolmitriptan increased the blood concentrations of zolmitriptan by over 50%. However, this did not influence the effects of zolmitriptan, and the authors suggest that no dosage adjustment is needed when these drugs are taken together.

Another study in healthy volunteers found that cimetidine increased the blood concentrations of zolmitriptan (5 mg) and prolonged its half-life. The authors of his study did suggest that the dosage of zolmitriptan may need to be reduced in patients taking cimetidine because of this reduction in metabolism. The same study found that rifampicin (Rifadin, Rimactane) did not interact with zolmitriptan.

RISKS AND PRECAUTIONS:[15] Triptans may cause temporary spasms of the arteries feeding the heart. This could produce symptoms similar to those seen in a heart attack. Some symptoms of reduced blood flow to the intestines may also appear. These effects sometimes require discontinuation of zolmitriptan. Because zolmitriptan is metabolized in the liver, it is used with caution in people with liver damage. Rat studies suggested that zolmitriptan or its other forms bind to melanin in the eye and accumulate. This may represent an increased risk of damage to the eye if zolmitriptan is used long-term. The influence of zolmitriptan on pregnancy and lactation is not known. Therefore, zolmitriptan is used during and after pregnancy only if the potential benefit justifies the potential risk to the child.

CLINICAL TRIALS[16]

The effectiveness of zolmitriptan tablets in the acute treatment of migraine headaches was demonstrated in five studies.

In all five studies, the percentage of patients achieving headache response two hours after treatment was significantly greater among patients receiving zolmitriptan at 2.5 and 5 mg doses compared to those who received placebo.

Pregnancy Category (US FDA)

Category C: Either studies in animals have revealed adverse effects on the foetus (teratogenic or embryocidal or there are no controlled studies in women or studies in women and animals are not available. Drugs should be given potential benefit justifies the potential risk to the foetus.

Breast-feeding

It is not known whether zolmitriptan is distributed into breast milk. Zolmitriptan was found to be distributed into the milk of lactating rats. The concentration of zolmitriptan in the rat milk was equivalent to maternal plasma concentrations at 1 hour and four times higher than maternal plasma concentrations at 4 hours.

Pediatrics

Appropriate studies on the relationship of age to the effects of zolmitriptan have not been performed in children up to 12 years of age.

Adolescents

Appropriate studies performed to date have not demonstrated pediatrics-specific problems that would limit the usefulness of zolmitriptan in adolescents.

Geriatrics

No information is available on the relationship of age to the effects of zolmitriptan in geriatric patients.

HOW ZOLMITRIPTAN IS TAKEN:[17]

Zolmitriptan is available in 2.5 mg and 5 mg doses. It is available in the form of tablets,Orally Disintegrating Tablets and nasal spray.Studies have shown that the higher dose is not necessarily more effective, but it may increase side effects. Dosing regimens usually start with the lower dose in order to assess safety. The higher dose is used if zolmitriptan is well-tolerated at the lower dose. Zolmitriptan is taken at the onset of migraine symptoms. If these symptoms return or are alleviated, another dose can be taken two hours after the first dose. Not more than 10 mg is taken within a 24-hour period.

ZOMIG Tablets: In controlled clinical trials, single doses of 1, 2.5 and 5 mg of ZOMIG Tablets were effective for the acute treatment of migraines in adults. A greater proportion of patients had headache response following a 2.5 or 5 mg dose then following a 1 mg dose. In the direct comparison of 2.5 and 5 mg, there was little added benefit from the larger dose but side effects are generally increased at 5 mg. Patients should, therefore, be started on 2.5 mg or lower. If the headache returns, the dose may be repeated after 2 hours, not to exceed 10 mg within a 24-hour period. Controlled trials have not adequately established the effectiveness of a second dose if the initial dose is ineffective. The safety of treating an average of more than three headaches in a 30-day period has not been established.

ZOMIG-ZMT Orally Disintegrating Tablets: In a controlled clinical trial, a single dose of 2.5 mg of ZOMIG-ZMT Tablets was effective for the acute treatment of migraines in adults. If the headache returns, the dose may be repeated after 2 hours, not to exceed 10 mg within a 24-hour period. Controlled trials have not adequately established the effectiveness of a second dose if the initial dose is ineffective. The safety of treating an average of more than three headaches in a 30-day period has not been established. Administration with liquid is not necessary. The orally disintegrating tablet is packaged in a blister. The blister pack should bepeeled open, and the orally disintegrating tablet placed on the tongue, where it will dissolve and be swallowed with the saliva. It is not recommended to break the orally disintegrating tablet.

ZOLMITRIPTAN PRESCRIBEDDOSE (tablets)

Usual adult and geriatric dose

Oral, initially 2.5 mg or lower (tablet may be broken in half).If necessary, additional doses may be taken at intervals of at least two hours.

A single dose of less than 2.5 mg is recommended for patients with hepatic disease or impairment.

Usual adult limits

10 mg in twenty-four hours.

Safety and efficacy have not been established in children under 18 years of age.

Strength(s) available

U.S.—2.5 mg (Rx) [Zomig (anhydrous lactose) (microcrystalline cellulose) (sodium starch glycolate) (magnesium stearate) (hydroxypropyl methylcellulose) (titanium dioxide) (polyethylene glycol 400) (yellow iron oxide) (red iron oxide) (polyethylene glycol 8000)]

5 mg (Rx) [Zomig (anhydrous lactose) (microcrystalline cellulose) (sodium starch glycolate) (magnesium stearate) (hydroxypropyl methylcellulose) (titanium dioxide) (polyethylene glycol 400) (yellow iron oxide) (red iron oxide) (polyethylene glycol 8000)]

Packaging and storage:

Store at room temperature, preferably between 20 and 25 ºC (68 and 77 ºF)

ZOLMITRIPTAN ORAL DISINTEGRATING TABLETS

Usual adult dose

Oral, initially 2.5 mg. If necessary, additional doses may be taken at intervals of at least two hours to a maximum of 10 mg in a twenty-four-hour period.

Note: Patients with moderate to severe hepatic function impairment should receive a low dose. Blood pressure monitoring is recommended.

Usual adult limits

10 mg in twenty-four hours.

Safety and efficacy have not been established in children under 18 years of age.

Strength(s) usually available

U.S.—2.5 mg (Rx) [Zomig-ZMT (Orally disintegrating tablets) (mannitol USP) (microcrystalline cellulose NF) (crospovidone anhydrous NF) (aspartame NF) (sodium bicarbonate USP) (citric acid anhydrousUSP) (colloidal silicon dioxide NF) (magnesium stearate NF) (orange flavor SN 027512)]{02}

Packaging and storage:

Store at controlled room temperature 20 to 25°C (68 to 77°F). Protect from light and moisture.

NASAL SPRAY: The rapid absorption of zolmitriptan nasal spray may explain the faster relief from migraine reported in patients compared with oral zolmitriptan. Many migraine patients experience nausea or vomiting during an attack and may find it difficult to take a tablet. Thus, non-oral routes of administration may be beneficial for acute migraine treatments in some patients. As an alternative to oral tablets, a nasal spray formulation of zolmitriptan has been developed.

Zolmitriptan has previously been shown to appear in plasma as early as 5 minutes after administration. The nasal spray also demonstrates a very fast onset of action, with high and sustained headache response rates, good pain-free rates and a good tolerability profile. Zolmitriptan was detected in plasma 2 minutes after intranasal administration in the majority of subjects (~75%) compared with 10 minutes after oral administration. The intranasal:tablet ratio for zolmitriptan area under the concentration-time curve from time zero to infinity was 0.924 (90% CI 0.826, 1.033) and 0.960 (90% CI 0.865, 1.066) for the 2.5 and 5mg doses, respectively. Other pharmacokinetic parameters were similar between the two formulations.

Dosage form	Route	Active Ingredient	Strength
Spray	Nasal	Zolmitriptan	5mg/spray
Tablets	Orodispersible	Zolmitriptan	2.5 & 5mg
Tablets	Oral	Zolmitriptan	2.5 & 5mg

Marketed formulations of zolmitriptan

TREATMENT OF OVERDOSE:[9]

Monitoring—Patients should be monitored for at least 15 hours after an overdose of zolmitriptan.

Supportive care—Maintaining an open airway and breathing, maintaining proper fluid and electrolyte balance, and/or correcting hypertension.

ZOLMITRIPTAN DISEASE INTERACTIONS:[9]

Cardiac diseases

1) 5-Ht1 Agonists (Includes Zolmitriptan) CAD Risk Factors:-

The group of drugs known as 5-hydroxytryptamine1 receptor (5-HT1) agonists can cause vasospastic reactions, including coronary vasospasm, peripheral vascular ischemia, and colonic ischemia. Rarely, serious adverse cardiac events including acute myocardial infarction, arrhythmia, cardiac arrest, and death have been reported within a few hours following the administration of 5-HT1 agonists, in some cases even in patients with no prior history or findings of coronary artery disease (CAD). Significant elevation in blood pressure, including hypertensive crisis, has also been reported on rare occasions in patients with and without a history of hypertension, as have transient increases in blood pressure and peripheral vascular resistance. In general, patients with potentially unrecognized CAD as predicted bythe presence of risk factors (e.g., hypertension, hypercholesterolemia, tobacco use, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) should not be administered 5-HT1 agonists unless a cardiovascular evaluation provides satisfactory clinical evidence indicating thelack of CAD, ischemic heart disease, or other significant underlying cardiovascular disease. As a precaution, the manufacturers recommend that the first dose be administered under medical surveillance in such patients, and that electrocardiographic monitoring be considered during the interval immediately following administration to help detect any asymptomatic cardiac ischemia that may occur. Periodic cardiovascular evaluations should be performed during intermittent, long-term use.

2) 5-Ht1 Agonists (Includes Zolmitriptan) Cardiovascular Disease:

The use of 5-hydroxytryptamine1 receptor (5-HT1) agonists is contraindicated in patients with a current or past history of ischemic cardiac, cerebrovascular, and/or peripheral vascular diseases. In addition, these agents should not be used in patients with significant underlying cardiovascular diseases or uncontrolled hypertension. 5-HT1 agonists can cause vasospastic reactions, including coronary vasospasm, peripheral vascular ischemia, and colonic ischemia. Rarely, serious adverse cardiac events including acute myocardial infarction, arrhythmia, cardiac arrest, and death have been reported within a few hours following the administration of 5-HT1 agonists, in some cases even in patients with no prior history or findings of coronary artery disease (CAD). Significant elevation in blood pressure, including hypertensive

crisis, has also been reported on rare occasions in patients with and without a history of hypertension, as have transient increases in blood pressure and peripheral vascular resistance. Cerebrovascular events have included cerebral hemorrhage, subarachnoid hemorrhage, and stroke, some resulting in fatalities. However, the relationship to 5-HT1 agonists is uncertain and, in a number of cases, the cerebrovascular events may have been primary where symptoms were mistaken to be migraine.

3) Zolmitriptan (Includes Zolmitriptan) Liver Disease:

The initial dose recommended for use in patients with hepatic dysfunction is 1.25 mgorally once. Significant elevations in blood pressure have been reported in some patients with moderate to severe liver dysfunction. Therefore, both a lower dose and blood pressure monitoring are recommended for patients with liver dysfunction.

Zolmitriptan is primarily metabolized by the liver. Following oral administration in patients with severe hepatic impairment, plasma concentrations of zolmitriptan were significantly increased (up to several-fold) compared to healthy controls. Some patients experienced 20 to 80 mm Hg elevations in systolic and/or diastolic blood pressure after a 10 mg dose, presumably due to drug accumulation. Therapy with zolmitriptan should be administered cautiously in patients with impaired hepatic function. Lower dosages, no more than 2.5 mg, as well as blood pressure monitoring should be considered in patients with moderate or severe hepatic impairment.

4) Zolmitriptan (Includes Zolmitriptan) Renal Dysfunction:

Zolmitriptan is excreted in the urine primarily as metabolites but also as unchanged drug. Following oral administration in patients with renal impairment, the clearance of zolmitriptan was not significantly altered in patients with moderate impairment (CrCl = 26 to 50 mL/min) but was reduced by 25% in patients with severe impairment (CrCl = 5 to 25 mL/min) compared to healthy controls. Therapy with rizatriptan should be administered cautiously in patients with significantly impaired renal function. A lower initial dosage may be appropriate

ALTERNATIVES:[9]

Several alternatives to zolmitriptan for the treatment of migraine attacks exist:

- Other triptans such as sumatriptan (Imitrex), [[[rizatriptan]] (Maxalt), naratriptan (Amerge), and almotriptan (Axert)
- Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (Advil, Motrin) or aspirin
- Ergots like ergotamine (Ergomar) and dihydroergotamine

- Anti-nausea medications like prochlorperazine (Compazine)
- Butalbital combinations
- Opiates like codeine

Recent DevelopmentsonZolmitriptan:

Lu-shanyu et al, studied the enzyme kinetics and drug interaction, the metabolism of

zolmitriptan and possible drug–drug interactions were investigated in rat hepatic microsomes induced with different inducers.An active metabolite, *N*-demethylzolmitriptan, was detected and another minor, inactive metabolite that was reported in humanhepatic microsomesThe

results of the inhibition experiments provided information for the interactions between zolmitriptan and drugs co-administratedin clinic, and it is helpful to explain the drug–drug interactions of clinical relevance on enzyme level. This study also demonstratedthat fluvoxamine may be a mechanism-based inactivator of CYP1A2.

Peter J. Goadsby et al, developed A nasal formulation that has clear evidencefor local absorption, resulting in plasma drug concentrations within 2 minutes of dosing, central nervous system penetration 3minutes later, and a significant efficacy benefit versus placebo 10 to 15 minutes after dosing. Intranasal zolmitriptan offers advantages to migraineurs, particularly those seeking a more rapid onset of effect without wishing to self-inject, or those with gastrointestinal upset. The comparison of pharmacokinetic and clinical data available from different formulations of zolmitriptan contributes both to the understanding of its mode of action and the characteristics required of an acute migraine treatment if it is to meet patient needs.

Xiaoyan Chena et al,has developed A sensitive and selective liquid chromatography–tandem spectrometry method for the determination of zolmitriptan was developed and validatedover the linearity range 0.05–30 ng/ml with 0.5 ml of plasmausing diphenhydramine as the internal standard. The mobile phase consisted of acetonitrile–water–formic acid (70:30:0.5), at a flow rateof 0.5 ml/min. In positive mode, zolmitriptan produced a protonated precursor ion at *m*/*z* 288 and a corresponding product ion at *m*/*z* 58. Andinternal standard produced a protonated precursor ion at *m*/*z* 256 and a corresponding product ion at *m*/*z*167.phenhydramine as the internal standard. The method had a lower limit of quantification of 0.05 ng/ml forzolmitriptan, which offered increased sensitivity and selectivity of analysis, compared with existing methods. The method was successfully appliedto a pharmacokinetic study of zolmitriptan after an oral administration of 5mg zolmitriptan to 20 healthy volunteers.

N.G.RaghavendraRao*, developed A simple, economical, sensitive and specific UV spectrophotometric method for the estimation of Zolmitriptan in bulk drug tablet dosage form. The optimum conditionsfor the analysis of the drug were established. The wavelength maxima (λmax) forzolmitriptan were found to be 226.5 nm. The linearity for this method was found to be in therange of 1-5µg/ml. The method showed high sensitivity with reproducibility in results.

DanavenaRambabu et al, developed and validated a simple, selective, linear, precise and accurate RP-HPLC method for assay of Zolmitriptan in tablet dosage form.. The mobile phase consisted of 0.01% triethylamine : acetonitrile : 0.02M NH4H2PO4; 28.2:25:46.8 (V/V/V),the detection wavelength was 225nm. The retention time for Zolmitriptan was 3.705 min. The percentage RSD for precision and accuracy of the method was found to be less than 2%. The method was validated as per the ICH guidelines. The method was successfully applied for routine analysis of Zolmitriptan in tablet dosage form.

REFERENCES

1. Rang H.P, Dale M.M, Ritter J.M, Flower R.J. "Pharmacology". Sixth Edition, Churchill Livingstone Elsevier, USA, 2007.

2. Tripathi K.D. "Essentials of Medical Pharmacology". Sixth Edition, Jaypee Brothers Medical Publishers Pvt Ltd, New Delhi, 2010.

3. Peter J. Goads by, Rager Yates., Zolmitriptan intranasal: A review of the pharamcokinetics and clinical efficacy, Headache. 46 (2006) 138-149.

4. M.D. Ferrari, K.I. Roon, R.B.Lipton, et al., Oral triptans (Serotonin 5-HT (1B/1D) agonists) in acute migraine treatment: A meta-analysis of 53 trials. Lancet 358 (2001) 1668.

5. IP ADDENDUM 2012. Page No: 2971

6. Zolmitriptan – Wikipedia (http://en.wikipedia.org/wiki/Zolmitriptan).

7. Zolmitriptan – Online library (http://onlinelibrary.wiley.com/doi/10.1038/sj.bjp.0704979/full).

8. Zolmitriptan – Faqs (http://www.faqs.org/patents/app/20100145064)

9. Zolmitriptan – Drugs (http://www.drugs.com/ppa/zolmitriptan.html)

10. Zolmitriptan – Drug Bank (http://www.drugbank.ca/drugs/DB00315)

11. Danavena R , Bhoomaiah B, Phani. R.S.CH, K Balamuralikrishna. Validated RP – HPLC method for the estimation of zolmitriptan in formulation. Pharmacophore.2011; 2(2):150-5.

12. Soloman GD, Cady RK, Klapper JA, Earl NL, Saper JR, Ramadan NM. Clinical efficacy and tolerability of 2.5 mg zolmitriptan for

the acute treatment of migraine. Neurology. 1997 Nov; 49(5):1219-56.

13. Zolmitriptan – Mims (http://www.mims.com/India/drug/info/zolmitriptan)

14. Zolmitriptan – Nlm (http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601129.html)

15. Zolmitriptan – Medscape (http://www.medscape.com/viewarticle/503118)

16. Martindale, The Complete Drug Reference, 35th ed. London: Pharmaceutical Press; 2006.

17. Rapoport AM, Ramadan AM, Adelman JU et al. Optimizing the dose of zolmitriptan for the acute treatment of migraine. Neurology.1997 Nov;49(5):1210-8.