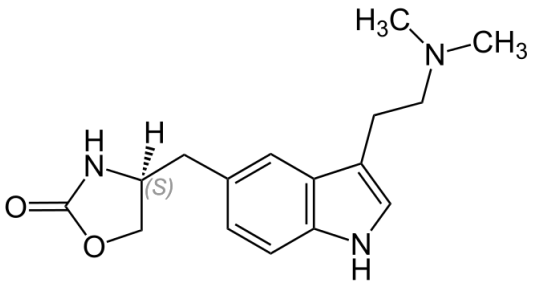
APO-ZOLMITRIPTAN TABLETS

NAME OF THE MEDICINE

Zolmitriptan.

Chemical Name: (*S*)-4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-2-oxazolidinone.

Structural Formula:



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

Molecular Weight: 287.36

CAS Registry Number: 139264-17-8

DESCRIPTION

Zolmitriptan is a white to almost white powder slightly soluble in water (1.3 mg/mL at 250°C) but shows greater solubility in 0.1M hydrochloric acid. Zolmitriptan has a pKa of 9.6. Zolmitriptan is a chiral molecule, which is synthesized as the *S* enantiomer.

Each tablet contains 2.5 mg zolmitriptan, as the active ingredient. In addition, each tablet also contains the following inactive ingredients: microcrystalline cellulose, lactose, sodium starch glycollate type A, magnesium stearate and Opadry complete film coating system 02G84574 Pink (hypromellose, titanium dioxide, macrogol 400, macrogol 8000, iron oxide red) (ARTG ID 108588).

PHARMACOLOGY

Pharmacological Actions

In pre-clinical studies, zolmitriptan has been demonstrated to be a selective agonist for the vascular human recombinant $5HT_{1B}$ and $5HT_{1D}$ receptor subtypes. Zolmitriptan is a high affinity $5HT_{1B/1D}$ receptor agonist with modest affinity for $5HT_{1A}$ receptors. Zolmitriptan has no significant affinity (as measured by radioligand binding assays) or pharmacological activity at $5HT_2$, $5HT_3$, $5HT_4$, α_1, α_2, or β_1, adrenergic; H_1, H_2, histaminic; muscarinic; dopaminergic$_1$, or dopaminergic$_2$ receptors. The N-desmethyl metabolite, 183C91, is also a $5HT_{1B/1D}$ agonist and is 2 to 6 times more potent, in animal models, than zolmitriptan. This metabolite shows higher *in vitro* affinity for $5HT_{1B/1D}$ receptors than zolmitriptan and also has modest affinity for $5HT_{1A}$ receptors.

It has been demonstrated that the pain sensitive structures of the cranial cavity in humans are the blood vessels and the vasculature of the dura mater. These tissues are innervated by trigeminal afferent fibres. In animal models the administration of zolmitriptan, with its agonist activity on the vascular $5HT_1$ receptors causes vasoconstriction associated with an inhibition of the release of calcitonin gene related peptide (CGRP), Vasoactive Intestinal Peptide (VIP) and substance P. These two events, vasoconstriction and inhibition of neuropeptide release are proposed to cause relief from the migraine attack, as reflected by an onset of pain relief within 1 hour of administration and relief of nausea and vomiting, photophobia and phonophobia associated with migraine.

In addition to these peripheral actions, experimental studies in animals suggest zolmitriptan has action on the central nervous system allowing access to both the peripheral and migraine centres in the brain stem which may explain the consistent effect over a series of attacks in a single patient. Vasodilatation is achieved with the activation of a reflex pathway mediated by trigeminal orthodromic

fibres and parasympathetic innervation of the cerebral circulation via the release of VIP as a main effector transmitter. It is suggested that zolmitriptan blocks this reflex pathway and the release of VIP.

Pharmacokinetics

Following oral administration of zolmitriptan tablets, it is rapidly and well absorbed (at least 64%). The mean absolute bioavailability of the parent compound is approximately 40% but there is some degree of intersubject variability.

In healthy subjects, when given as a single dose, zolmitriptan and its active metabolite 183C91, display dose-proportional AUC and C_{max} over the dose range 2.5 to 50 mg. Absorption is rapid with 75% of C_{max} achieved within 1 hour and plasma concentrations are sustained subsequently for 4 to 6 hours. Zolmitriptan absorption is unaffected by the presence of food. There is no evidence of accumulation on multiple dosing of zolmitriptan.

Plasma concentration of zolmitriptan and its metabolites are lower in the first 4 hours after drug administration during a migraine compared with a migraine-free period, suggesting delayed absorption consistent with the reduced rate of gastric emptying observed during a migraine attack.

Zolmitriptan is eliminated largely by hepatic biotransformation followed by urinary excretion of the metabolites. There are three major metabolites: the indole acetic acid (the major metabolite in plasma and urine), the N-oxide and N-desmethyl analogues. The N-desmethylated metabolite (183C91) is active whilst the others are not. Plasma concentrations of 183C91 are approximately half those of the parent drug, hence it would therefore be expected to contribute to the therapeutic action. Over 60% of a single oral dose is excreted in the urine (mainly as the indoleacetic acid metabolite) and about 30% in faeces mainly as unchanged parent compound.

A study to evaluate the effect of liver disease on the pharmacokinetics of zolmitriptan showed that the AUC and C_{max} were increased by 94% and 50% respectively in patients with moderate liver disease and by 226% and 47% in patients with severe liver disease compared with healthy volunteers. Exposure to the metabolites, including the active metabolite, was decreased. For the 183C91 metabolite, AUC and C_{max} were reduced by 33% and 44% in patients with moderate liver disease and by 82% and 90% in patients with severe liver disease.

The plasma half-life (T½) of zolmitriptan was 4.7 hours in healthy volunteers, 7.3 hours in patients with moderate liver disease and 12 hours in those with severe liver disease. The corresponding T½ values for the 183C91 metabolite were 5.7 hours, 7.5 hours and 7.8 hours respectively.

Following intravenous administration, the mean total plasma clearance is approximately 10 mL/min/kg, for the parent drug, of which one quarter is renal clearance. Renal clearance is greater than glomerular filtration rate suggesting renal tubular secretion. The volume of distribution for the parent drug following i.v. administration is 2.4 L/kg.

Plasma protein binding of zolmitriptan and the N-desmethyl metabolite is low (approximately 25%). The mean elimination half-life of zolmitriptan is 2.5 to 3 hours. The half-lives of its metabolites are similar, suggesting their elimination is formation-rate limited.

Renal clearance of zolmitriptan and its metabolites is reduced (7 to 8 fold) in patients with moderate to severe renal impairment compared to healthy subjects, although the AUC of the parent compound and the active metabolite were only slightly higher (16 and 35% respectively) with a 1 hour increase in half-life to 3 to 3.5 hours. These parameters are within the ranges seen in healthy volunteers.

In a small group of healthy individuals, there was no pharmacokinetic interaction with ergotamine. Concomitant administration of zolmitriptan with ergotamine/caffeine was well tolerated and did not result in any increase in adverse events or blood pressure changes as compared to zolmitriptan alone.

Following administration of moclobemide, a specific MAO-A inhibitor, there was a small increase (26%) in AUC for zolmitriptan and a 3 fold increase in AUC of the active metabolite. Therefore, a maximum intake of 5 mg zolmitriptan in 24 hours, is recommended in patients taking a MAO-A inhibitor. The drugs should not be used together if doses of moclobemide higher than 150 mg b.i.d. are administered.

Selegiline, a MAO-B inhibitor, and fluoxetine, a selective serotonin reuptake inhibitor (SSRI), had no effect on the pharmacokinetic parameters of zolmitriptan.

The pharmacokinetics of zolmitriptan in healthy elderly subjects were similar to those in healthy young volunteers.

CLINICAL TRIALS

Treatment of Acute Migraine, with or without Aura, with zolmitriptan tablets

Overall there were 4,003 unique individuals who participated in the zolmitriptan clinical development. A total of 3,096 unique individuals were exposed to zolmitriptan. Of this total, 316 unique individuals were accounted for in Clinical Pharmacology studies; 2,633 in placebo-controlled treatment of migraine studies, 79 in the long term multiple attack study (Study 015; 2,058 subjects in total, 79 of whom were unique subjects not previously exposed to zolmitriptan) 38 in two uncontrolled patient treatment studies; and 30 in an acute prevention of migraine study. In addition 524 unique individuals were exposed to placebo (119 in clinical pharmacology studies, 401 in treatment of migraine studies).

These subjects received almost 50,000 oral doses of zolmitriptan. Across all patient studies, a total of 34,296 attacks were treated with zolmitriptan. The majority of these (31,579) were treated in a long-term study.

In patient studies, the protocol inclusion criteria required patients to have an established diagnosis of migraine, with or without aura (as defined by the International Headache Society criteria). Patients had a migraine history of at least 1 year with an age of onset less than 50 years and had one to six migraines per month over the preceding 6 months. In addition, patients had to have screening laboratory values within acceptable ranges and be without evidence of ischaemic heart disease, arrhythmia, or accessory pathways, based on a 12-lead ECG. The age range of patients was 18-65 years in most studies.

The first of the pivotal studies was a Phase II study of almost 1,200 patients comparing zolmitriptan (n = 900) to placebo. The response rates at 2 hours in patients receiving placebo, zolmitriptan 5 mg, 10 mg, 15 mg and 20 mg were 21%, 61%, 67%, 67% and 74%, respectively. The response rate had been slightly lower at 1h post-dosing, being 16% in the group receiving placebo and 44-50% in the groups treated with zolmitriptan. The percentage of patients with no pain at 2 hours was 1% in the placebo group, and 39%, 39%, 43% and 47% in the zolmitriptan 5 mg, 10 mg, 15 mg and 20 mg groups, respectively. The placebo group also showed a far greater recurrence rate over 24 hours than the zolmitriptan groups, with median time to recurrence being 4.5 hours with placebo and 15.3 hours with zolmitriptan.

The incidence of adverse events was proportional to dose, and consisted predominantly of asthenia, heaviness (in the chest, limbs, head), nausea, paraesthesia, a feeling of warmth, dizziness, somnolence, vertigo and dry mouth. Of the cardiovascular events, 34 were noted with zolmitriptan versus 1 with placebo, but there was only 1 serious adverse event (tachycardia in a patient with a pre-existing condition of Wolff-Parkinson-White syndrome (see **PRECAUTIONS**).

The phase III study also investigated approximately 1,200 patients, but included lower doses of zolmitriptan (1 mg, 2.5 mg, 5 mg and 10 mg). The findings indicated that the response to zolmitriptan 1 mg was greater than the response to placebo, however no difference between placebo and zolmitriptan 1 mg was found in another study. The 2.5 mg dose was associated with a response rate of 63% versus 65% with the 5 mg dose, suggesting that these two dose levels were equi-effective. This study also showed the incidence of nausea to be reduced significantly with zolmitriptan treatment when compared with placebo. The safety profile of zolmitriptan was similar to that observed in the previous trials. There were no serious adverse events reported in this selected trial population.

INDICATIONS

Zolmitriptan is indicated for the acute treatment of migraine with or without aura.

CONTRAINDICATIONS

Zolmitriptan is contraindicated in the following cases:

- Hypersensitivity to any component of the product.
- A history of myocardial infarction.
- Ischaemic heart disease; Prinzmetal angina/coronary vasospasm; peripheral vascular disease; symptoms or signs consistent with ischaemic heart disease.
- Moderate or severe hypertension and mild uncontrolled hypertension.
- Moderate or severe hypertension and mild uncontrolled hypertension.
- Other $5HT_{1D}$ receptor agonists should not be used concomitantly with zolmitriptan.
- Creatinine clearance of less than 15 mL/min.
- On theoretical grounds (see **PHARMACOLOGY**), zolmitriptan should not be administered to patients with a history of cerebrovascular accident (CVA) or transient ischaemic attack (TIA).

PRECAUTIONS

Cerebrovascular events have been reported in patients treated with $5HT_1$ agonists, some resulting in fatalities. In a number of cases, it appears that the cerebrovascular events were primary, the agonist having been administered in the incorrect belief that the symptoms were a consequence of the migraine. Zolmitriptan should only be used when a clear diagnosis of migraine has been established. Care should be taken to exclude other potentially serious neurological conditions. There are no data on the use of zolmitriptan in hemiplegic or basilar migraine

Migraneurs may be at risk of certain cerebrovascular events. Cerebral haemorrhage, subarachnoid haemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with $5HT_1$ agonists.

There have been rare reports of anaphylaxis/anaphylactoid reactions in patients receiving zolmitriptan.

Zolmitriptan should not be given to patients with symptomatic Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathways.

This class of compounds ($5HT_{1B}/_{1D}$ agonists) has been associated with coronary vasospasm, angina pectoris and myocardial infarction. In very rare cases this has occurred with zolmitriptan. In patients with risk factors for ischaemic heart disease, cardiovascular evaluation prior to commencement of treatment with this class of compounds, including zolmitriptan, is recommended (see **CONTRAINDICATIONS**). These evaluations, however, may not identify every patient who has cardiac disease, and in very rare cases, serious cardiac events have occurred in patients without underlying cardiovascular disease.

As with other $5HT_{1D}$ agonists, atypical sensations over the precordium (see **ADVERSE EFFECTS**) have been reported after the administration of zolmitriptan. Where such symptoms are thought to indicate ischaemic heart disease, no further doses of zolmitriptan should be given and appropriate evaluation carried out.

Serotonin Syndrome has been reported with combined use of triptans, and Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin Noradrenaline Reuptake Inhibitors (SNRIs). Serotonin Syndrome is a potentially life-threatening condition, and it may include signs and symptoms such as: mental status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood-pressure, hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, in-coordination, weakness), and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea). Careful observation of the patient is advised when zolmitriptan is administered with an SSRI or SNRI, particularly during treatment initiation and dosage increases (see **INTERACTIONS WITH OTHER MEDICINES**).

Transient increases in systemic blood pressure (which may be more pronounced in the elderly) have been reported in patients with and without a history of hypertension; very rarely these increases in blood pressure have been associated with significant clinical events.

Effects on Fertility

A fertility study by the oral route of administration, during which male and female rats were dosed daily with zolmitriptan prior to and throughout the mating period, showed no evidence of impaired fertility at doses producing plasma concentrations greater than 100 times those attained in humans after the maximum recommended daily dose of 10 mg (based on AUC).

Use in Pregnancy (Category B3)

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

There are no adequate and well-controlled studies in pregnant women. Studies in rats and rabbits treated with oral zolmitriptan during organogenesis, showed no direct teratogenic effects. Plasma concentrations in rats and rabbits receiving the highest doses were greater than 100 times and 40 times, respectively, the exposure (based on AUC) attained in humans after the maximum recommended daily dose of 10 mg. Administration of zolmitriptan should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

Use in Lactation

Studies have shown that zolmitriptan passes into the milk of lactating animals. No data exist for passage of zolmitriptan into human breast milk. Therefore, caution should be exercised when administering zolmitriptan to women who are breast-feeding.

Genotoxicity

Zolmitriptan showed no evidence of genotoxicity in a series of assays for gene mutations (bacteria and Chinese hamster ovary cells). Tests for chromosomal damage in human lymphocytes *in vitro*, showed that zolmitriptan was clastogenic, however, zolmitriptan was not clastogenic *in vivo*.

Carcinogenicity

In carcinogenicity studies, rats and mice were given zolmitriptan by oral gavage for 104 and 92 weeks, respectively. Average plasma concentrations in rats and mice receiving the highest doses were greater than 100 times the exposure (based on AUC) attained in humans after the maximum recommended daily dose of 10 mg. The rat study revealed an increased incidence of thyroid follicular cell adenoma at the highest dose tested, thought to be due to enhanced hepatic thyroxine clearance. There was no evidence of an increased incidence of tumours in the mouse.

Effect on Laboratory Tests

Zolmitriptan is not known to interfere with commonly employed clinical laboratory tests.

INTERACTIONS WITH OTHER MEDICINES

There is no evidence that concomitant use of migraine prophylactic medications has any effect on the efficacy or unwanted effects of zolmitriptan (for example beta blockers, oral dihydroergotamine, pizotifen).

The pharmacokinetics and tolerability of zolmitriptan were unaffected by acute symptomatic treatments such as paracetamol, metoclopramide and ergotamine. Concomitant administration of other 5HT1D agonists within 24 hours of zolmitriptan treatment should be avoided.

Data from healthy subjects suggest there are no pharmacokinetic or clinically significant interactions between zolmitriptan and ergotamine. However, the increased risk of coronary vasospasm is a theoretical possibility, and concomitant administration is contraindicated. It is advised to wait at least 24 hours following the use of ergotamine containing preparations before administering zolmitriptan. Conversely it is advised to wait at least six hours following use of zolmitriptan before administering an ergotamine containing product.

The major metabolite of zolmitriptan, the indole acetic acid (2161W92), is derived from the active metabolite, N-desmethyl zolmitriptan (183C91), by the action of monoamine oxidase A. This is evidenced by the effects of co-administration of the selective MAO-A inhibitor, moclobemide, which

resulted in a 3-fold increase in the exposure to 183C91 but had minimal effects (increase of 26% in AUC) on zolmitriptan levels. (The metabolite 183C91 is also a 5HT1D agonist with higher receptor affinity than the parent drug and therefore contributes to the overall effect after zolmitriptan administration). Hence, in patients taking a MAO-A inhibitor (selective or non-selective), a maximum intake of 5 mg zolmitriptan in 24 hours is recommended.

Following the administration of cimetidine, a general P450 inhibitor, the half-life of zolmitriptan was increased by 44% and the AUC increased by 48%. In addition, the half-life and AUC of the active, N-desmethylated, metabolite (183C91) were doubled. A maximum dose of 5 mg zolmitriptan in 24 hours is recommended in patients taking cimetidine. Based on the overall interaction profile, an interaction with inhibitors of the cytochrome P450 isoenzyme CYP1A2 cannot be excluded. Therefore, the same dosage reduction is recommended with compounds of this type, such as fluvoxamine and the quinolone antibiotics (e.g. ciprofloxacin). Following the administration of rifampicin, no clinically relevant differences in the pharmacokinetics of zolmitriptan or its active metabolite were observed.

Cases of life-threatening syndrome have been reported during combined use of triptans and SSRIs (e.g. fluoxetine, fluvoxamine, paroxetine, sertraline) and SNRIs (e.g. venlafaxine) (see **PRECAUTIONS**).

As with other $5HT_{1B}/_{1D}$ agonists, there is a potential pharmacodynamic interaction with the herbal remedy, St. John's Wort (*Hypericum perforatum*), which may result in an increase in undesirable effects.

Effects on Ability to Drive and Use Machines

Even though there was no significant impairment of psychomotor test performances in healthy volunteers following doses of up to 20 mg, somnolence was reported in pharmacological and clinical trials. Caution is recommended in patients performing skilled tasks (e.g. driving or operating machinery) as drowsiness and other symptoms may occur during a migraine attack and following treatment.

ADVERSE EFFECTS

Zolmitriptan is well tolerated. Adverse reactions are typically mild/moderate, transient, not serious and resolve spontaneously without additional treatment. The adverse event profile has been demonstrated to be similar for the administration of either 2.5 mg or 5 mg of zolmitriptan.

Possible adverse reactions tend to occur within four hours of dosing and are no more frequent following repeated dosing; certain symptoms may be considered to be part of the migraine attack itself.

Clinical Trial Data

The incidence of adverse drug reactions associated with zolmitriptan therapy is tabulated below according to the format recommended by the Council for International Organisations of Medical Sciences (CIOMS III working Group; 1995).

Table 1: Adverse Drug Reactions Reported in Zolmitriptan Clinical Trials

Frequency	System Organ Class	Event
Common (≥ 1% – < 10%)	Nervous system disorders	Abnormalities or disturbances of sensation; dizziness; headache; hyperaesthesia; paraesthesia; somnolence; warm sensation
	Cardiac disorders	Palpitations
	Gastrointestinal disorders	Abdominal pain; dry mouth; nausea; vomiting
	Musculo-skeletal and connective tissue disorders	Muscle weakness; myalgia
	General disorders	Asthenia; Heaviness, tightness, pain or pressure in throat, neck, limbs or chest
Uncommon (≥ 0.1% – < 1%)	Cardiac disorders	Tachycardia
	Vascular disorders	Transient increases in systemic blood pressure*

Frequency	System Organ Class	Event
	Renal and urinary disorders	Polyuria; increased urinary frequency
Rare (≥ 0.01% – < 0.1%)	Immune system disorders	Anaphylaxis/anaphylactoid reactions; hypersensitivity reactions
	Skin and subcutaneous disorders	Angioedema; urticaria
Very rare (< 0.01%)	Cardiac disorders	Angina pectoris; coronary vasospasm; myocardial infarction
	Gastrointestinal disorders	Bloody diarrhoea; gastrointestinal infarction or necrosis; gastrointestinal ischaemic events; ischaemic colitis; splenic infarction
	Renal and urinary disorders	Urinary urgency

* May be more pronounced in the elderly; reported in patients with and without a history of hypertension.

Zolmitriptan tablet (2.5 mg and 5 mg) controlled clinical studies

Table 2 lists the adverse events that occurred in ≥ 2% of the patients in any one of the zolmitriptan (2.5 mg and 5 mg) or sumatriptan 100 mg dose groups of the controlled clinical trials. Only events that were more frequent in a treatment group compared to the placebo groups are included.

Table 2: Adverse Experience Incidence in five Placebo-controlled Migraine Clinical Trials: Events reported by ≥ 2% Patients treated with Zolmitriptan or Sumatriptan

Adverse Event Type	Placebo (n = 401)	Zolmitriptan 2.5 mg (n = 498)	Zolmitriptan 5 mg (n = 1012)	Sumatriptan 100 mg (n = 504)
ATYPICAL SENSATIONS	7%	12%	17%	15%
Hypaesthesia	1%	1%	2%	1%
Paraesthesia (all types)	2%	6%	8%	7%
Sensation warm/cold	4%	5%	7%	7%
PAIN AND PRESSURE SENSATIONS	7%	17%	25%	26%
Chest – pain/tightness/pressure and/or heaviness	1%	3%	4%	5%
Neck/throat/jaw – pain/tightness/pressure	3%	7%	10%	11%
Heaviness other than chest or neck	1%	2%	5%	5%
Pain – location specified	1%	2%	3%	1%
Other – Pressure/tightness	1%	3%	3%	4%
DIGESTIVE	8%	16%	14%	14%
Dry Mouth	2%	3%	3%	2%
Dyspepsia	1%	2%	1%	1%
Dysphagia	0%	0%	2%	1%
Nausea	4%	9%	6%	7%
NEUROLOGICAL	10%	17%	21%	18%
Dizziness	4%	8%	10%	7%
Somnolence	3%	6%	8%	6%
Vertigo	0%	0%	2%	3%
OTHER				
Asthenia	3%	3%	9%	11%
Palpitations	1%	< 1%	2%	2%
Mylagia	< 1%	1%	2%	1%
Myasthenia	< 1%	1%	2%	1%
Sweating	1%	2%	3%	2%

Other adverse events reported less frequently are listed below; these are classified by body system categories and given in order of decreasing frequency, using the definitions: uncommon - occurring in 1/100 – 1/1,000 patients; rare - occurring in fewer than 1/1,000 patients. All reported events are included except those already listed in the table above, those too general to be informative and those not reasonably associated with the use of the drug.

Atypical sensation

Uncommon: hyperaesthesia of the mouth and skin.

General

Uncommon: allergy reaction, chills, facial oedema, fever, malaise and photosensitivity.

Cardiovascular

Uncommon: arrhythmias, hypertension and syncope.
Rare: bradycardia, extrasystoles, postural hypotension, QT prolongation, tachycardia and thrombophlebitis.

Digestive

Uncommon: increased appetite, tongue oedema, oesophagitis, gastroenteritis, liver function abnormality and thirst.
Rare: anorexia, constipation, gastritis, haematemesis, pancreatitis, melena and ulcer.

Haemic

Uncommon: ecchymosis.
Rare: cyanosis, thrombocytopenia, eosinophilia and leucopoenia.

Metabolic

Uncommon: oedema.
Rare: hyperglycaemia and alkaline phosphatase increased.

Musculoskeletal

Uncommon: back pain, leg cramps and tenosynovitis.
Rare: arthritis, tetany and twitching.

Neurological

Uncommon: agitation, anxiety, depression, emotional lability and insomnia.
Rare: akathisia, amnesia, apathy, ataxia, dystonia, euphoria, hallucinations, cerebral ischaemia, hyperkinesia, hypotonia, hypertonia and irritability.

Respiratory

Uncommon: were bronchitis, bronchospasm, epistaxis, hiccup, laryngitis and yawn.
Rare: apnoea and voice alteration.

Skin

Uncommon: pruritus, rash and urticaria.

Special senses

Uncommon: dry eye, eye pain, hyperacusis, ear pain, parosmia and tinnitus.
Rare: diplopia and lacrimation.

Urogenital

Uncommon: haematuria, cystitis, polyuria, urinary frequency, urinary urgency.
Rare: miscarriage and dysmenorrhoea.

Post-Marketing Data

See **Adverse Effects**.

DOSAGE AND ADMINISTRATION

The recommended initial dose of zolmitriptan to treat a migraine attack is 2.5 mg.

The tablet should be swallowed whole with water.

If symptoms of migraine persist or recur within 24 hours of an initial response, a second dose may be taken. If a second dose is required, it should not be taken within 2 hours of the initial dose.

If a patient does not achieve satisfactory relief with 2.5 mg doses, subsequent attacks can be treated with 5 mg doses of zolmitriptan.

The onset of action in responders is apparent within 1 hour of dosing.

Zolmitriptan is equally effective whenever the tablets are taken during a migraine attack, although it is advisable that tablets are taken as early as possible after the onset of migraine headache.

In the event of recurrent attacks, it is recommended that the total intake of zolmitriptan, in a 24 hour period, should not exceed 10 mg.

Zolmitriptan is not indicated for prophylaxis of migraine.

Patient Sub-groups

Zolmitriptan is consistently effective in migraine, with or without aura, and in menstrually-associated migraine. The efficacy of zolmitriptan is also unaffected by gender, duration of the attack, pre-treatment nausea and concomitant use of common prophylactic migraine drugs.

Children

The efficacy of zolmitriptan tablets was not established in a placebo-controlled clinical trial for patients aged 12 to 17 years. The efficacy and safety of zolmitriptan in paediatric patients below 12 years have not been evaluated.

Adults including the Elderly

The safety and efficacy of zolmitriptan in individuals aged over 65 years have not been systematically evaluated. Use of zolmitriptan in the elderly is therefore not recommended.

Use in Adults with Hepatic Impairment

Although metabolism is reduced in patients with mild or moderate hepatic impairment (see **PHARMACOLOGY, Pharmacokinetics**), no dosage adjustment is required. However, for patients with severe hepatic impairment a maximum dose of 5 mg in 24 hours is recommended.

Use in Adults with Renal Impairment

A study was carried out in patients with creatinine clearances from 5 to 39 mL/min. No dosage adjustment required (see **PHARMACOLOGY, Pharmacokinetics**).

OVERDOSAGE

Volunteers receiving single oral doses of 50 mg commonly experienced sedation.

The elimination half-life of zolmitriptan tablets is 2.5 to 3 hours, (see **PHARMACOLOGY, Pharmacokinetics**) and therefore monitoring of patients after overdose with zolmitriptan tablets 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 haemodialysis or peritoneal dialysis has on the serum concentrations of zolmitriptan.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

PRESENTATION AND STORAGE CONDITIONS

APO-Zolmitriptan tablets are intended for oral administration.
Each tablet contains 2.5 mg zolmitriptan, as the active ingredient.

2.5 mg tablet:

Light pink, round, film-coated tablets, debossed with '2.5' on one side and plain on the other.

Blister pack (aluminium foil/aluminium foil) of 2 or 6 tablets (AUST R 200878).
Not all pack sizes may be available.

Storage

Store below 25°C.

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine.

NAME AND ADDRESS OF THE DISTRIBUTOR

Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park NSW 2113

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Date of first inclusion in the ARTG: 19 June 2013

Date of most recent amendment: 16 June 2014