6 DRUG PROFILE

6.1 Naratriptan Hydrochloride (NH)

6.1.1 Drug class: Antimigraine

6.1.2 Proprietary Name: Amerge

6.1.3 IUPAC Name: N-methyl-2-[3-(1-methylpiperidin-4-yl)-1H-indol-5-yl]ethane-1-sulfonamide

6.1.4 Molecular weight and CAS number:
   - Average: 335.464
     Monoisotopic: 335.166747749
   - CAS number: 121679-13-8

6.1.5 Formula: C₁₇H₂₅N₃O₂S

6.1.6 Structure:

6.1.7 Description

This compound belongs to the class of organic compounds known as indoles. These are compounds containing an indole moiety, which consists of pyrrole ring fused to benzene to form 2,3-benzopyrrole.
6.1.8 Physical, chemical and biological properties

- **Dissociation Constant:** pKa (Strong acidic) 11.5
  pKa (Strong basic) 9.18
- **Water solubility:** 35mg/ml
- **Log P:** 1.6
- **6.1.5 Melting Point:** 237-239°C (246 °C hcl salt)
- **Half–life:** 5-8 h
- **Volume of Distribution:** Approximately 170 L
- **Clearance:** 6.6 mL/min/kg
- **Protein binding:** 28% - 31% (over the concentration range of 50 to 1000 ng/mL)

6.1.9: Pharmacology

6.1.9.1: Mechanism of action

There are three basic distinctive pharmacological actions concerned in the antimigraine effect of the triptans:
1. Stimulation of presynaptic 5-HT_{1D} receptors, which serves to inhibit both dural vasodilation and inflammation.
2. Direct inhibition of trigeminal nuclei cell excitability via 5-HT_{1B/1D} receptor agonism in the brainstem and
3. Vasoconstriction of meningeal, dural, cerebral or pial vessels as a result of vascular 5-HT_{1B} receptor agonism. [1]

6.1.9.2: Pharmacodynamic:

Naratriptan is a selective agonist of serotonin (5-hydroxytryptamine; 5-HT) type 1B and 1D receptors which is structurally and pharmacologically related to other selective 5-HT_{1B/1D} receptor agonist having weak affinity for 5-HT_{1A}, 5-HT_{5A}, and 5-HT_{7} receptors and no significant affinity or pharmacological activity at 5-HT_{2}, 5-HT_{3} or 5-HT_{4} receptor subtypes or at alpha_{1}-, alpha_{2}-, or beta-adrenergic, dopamine_{1}, dopamine_{2}; muscarinic, or benzodiazepine receptors. This action in humans correlates
with the relief of migraine headache. In vitro and in vivo data suggest that Naratriptan has highest potency at the vascular $\text{5HT}_{1\beta}$ which mediate vasoconstriction.

In the studies on the anaesthetized dogs, Naratriptan tends to causes the selective vasoconstriction of carotid arterial bed while subcutaneously Naratriptan didn’t produce any change in global or regional cerebral blood flow in migraine patient. Naratriptan is supposed to have greater accessibility into the CNS effectively than sumatriptan as it is more lipophilic than Sumatriptan. Experimental data from animal studies also indicated the vasoconstriction, showing the activity on $\text{5-HT}_1$ receptors on peripheral terminals of the trigeminal nerve innervating cranial blood vessels, which may also contribute to the antimigrainous effect of Naratriptan in humans.

Naratriptan produced concentration-dependent contractions in isolated ring preparations of dog basilar and middle cerebral arteries. Potency of Naratriptan in terms of this effect was similar to that of serotonin and approximately 3-fold greater than that of sumatriptan. However, each agonist caused a similar maximum contraction.

Sagittal sinus-evoked activity in the trigeminal nucleus of anaesthetised cats was inhibited when given by intravenous administration. This effect was blocked by the $\text{5HT}_{1\beta/1\delta}$ antagonist, which suggests that, in part, the clinical action of Naratriptan is mediated through $\text{5HT}_{1\beta/1\delta}$ receptors located on the trigeminal neurons.

Subcutaneous naratriptan (1, 5 and 10 mg) had no statistically or clinically significant effect on forearm blood flow in a randomised, double-blind, placebo-controlled, 4-way crossover study involving 19 patients with a history of migraine.

Human volunteers were given two doses of oral naratriptan (1 plus 1 mg, 2.5 plus 2.5 mg, and 5 plus 5 mg) separated by 2 h indicated no significant effect on systolic blood pressure in a placebo-controlled, 4-way crossover trial involving 12 healthy male volunteers. Although small increases in weighted mean diastolic blood pressures were observed with doses of 2.5 plus 2.5 mg and 5 plus 5 mg, these increases were not considered clinically significant at doses of 2.5 plus 2.5 mg. A similar study that assessed the effects of subcutaneous Naratriptan found that doses of 1, 2.5 and 5mg were associated with respective increases in mean peak systolic blood pressures of 8, 15 and 15 mm Hg.
Naratriptan did not cause significant changes in heart rate or ECG morphology in studies involving healthy volunteers, patients with migraine and patients with suspected coronary artery disease [2 - 4].

### 6.1.9.3 Absorption

Well absorbed (74% oral bioavailability), absorption is rapid with peak plasma concentrations after 2-5 h. The rate of absorption is slower during a migraine attack [5].

### 6.1.9.4 Drug metabolism and pharmacokinetics

Naratriptan is metabolized by a wide range of cytochrome P-450 isoenzymes into a number of inactive metabolites. The main route of elimination is by renal excretion and metabolism in the liver through P-450 enzyme system metabolizing through the monoamine oxidase (MAO) system. Naratriptan has higher bioavailability range for 63 to 74 % respectively for women and men. Mean elimination half-life (t½) was reported to be about 6 h in both males and females (n = 23) after an oral dose of 5mg Naratriptan.

Naratriptan was predominantly eliminated by urinary excretion as unchanged drug (50% Naratriptan) and metabolites (30%). After an oral dose of 5mg, C_max and AUC values were 16.6 µg/L and 164 µ/L/h in females compared with 10.811µL and 108 µ/L/h in males. However, t_max values were similar in males and females after 3 h. Mean plasma clearance after an oral dose of naratriptan was 46.2 L/h in men compared with 30.5 L/h in women. Values after intravenous administration of naratriptan 1.5mg were 28.3 L/h in men and 22.6 L/h in women. Greater oral clearance in men than in women accounts for the gender differences in AUC and C_max values. Mean values for renal clearance after oral and intravenous administration were similar in men and women and ranged between 13.2 and 13.9 L/h. Renal clearance represented 49% of systemic clearance in men and 60% in women [6 – 8].
6.1.9.5 Clinical trials

According to the design six hundred thirteen migraineurs were diagnosed according to International Headache Society criteria and were treated with single migraine attack with Naratriptan tablets (2.5 mg, 1 mg, 0.25 mg, or 0.1 mg) or placebo in a randomized, double-blind, placebo-controlled, parallel-group study conducted at 54 United States centers. At dosing and at predetermined intervals beginning 30 minutes postdose, patients recorded migraine pain severity, clinical disability, and presence of associated migraine symptoms. Safety measures included adverse events, physical examinations, vital signs, ECGs, and clinical laboratory tests.

The results recorded indicated that headache relief (moderate or severe pain at dosing reduced to mild or no pain) 4 h postdose was reported in 60% of patients receiving Naratriptan 2.5 mg compared with 50%, 35%, 32%, and 34% of patients receiving Naratriptan 1 mg, 0.25 mg, 0.1 mg, and placebo, respectively. Clinical disability was reported after 4 h post dose as mild or none for 70% of patients receiving Naratriptan 2.5 mg compared with 63%, 47%, 48%, and 48% of patients receiving Naratriptan 1 mg, 0.25 mg, 0.1 mg, or placebo, respectively. Headache relief for each dose after four h was reported for efficacy for absence of nausea, photophobia, and phonophobia. With every dose Naratriptan adverse profile event was similar to that of placebo. From the clinical results generated it can be concluded that Naratriptan is effective and can be well tolerated for the acute treatment of migraine whereas 2.5 mg of dose was optimized for better efficacy and tolerability than other dosage studied [9 - 11].

6.1.9.6 Dose

Acute migraine with or without aura in adults: 1 to 2.5 mg orally with fluid. If the headache returns or if the patient has only a partial response, the dose may be repeated once after 4 h. The safety of treating more than four headaches in a 30 day period has not been established. The dose should not be consumed to patients with hemiplegic or basilar migraine.
6.1.9.7 Toxicity

Symptoms of overdose include light-headedness, loss of coordination, tension in the neck, and tiredness.

6.1.9.10 Tolerability:

No any incidence of adverse events was observed to increase with administration of a second dose of study medication for a given attack. From the reports it is depicted that incidence of side effects of triptan 5-HT agonists were low and showed no any difference placebo among the patients taking Naratriptan 2.5 mg and 1 mg. The adverse events experienced in more that 2% of attacks thronght out the year were indicated with nausea, hyposalivation, and drowsiness. The other side effects included were chest pressure, chest pain, warm sensation, numbnesss, tingling, were repoted infrequently event in 1% attacks treated with 2.5 mg Naratriptan tablets. Doses more than 2.5 mg (5 to 10 mg) were associated with a greater incidence of adverse events than placebo.

The incidence of adverse events associated with Naratriptan was decreased on prolonged use. 41% of patients experienced adverse events with naratriptan in the first 3 months of therapy, compared with 28% in the second 3-month period. [12 – 15]
6.2 Eletriptan Hydrobromide

6.2.1 Drug class: Antimigraine

6.2.2 Proprietary Name: Relpax

6.2.3 IUPAC Name: 5-[2-(benzenesulfonyl)ethyl]-3-[(2R)-1-methylpyrrolidin-2-yl]methyl]-1H-indole

6.2.4 Formula: C_{22}H_{26}N_{2}O_{2}S

6.2.5 Category: Serotonin Antagonists, Serotonin Receptor Agonists, Antimigraine agent.

6.2.6 Molecular Weight and CAS number

- Average: 382.519  Monoisotopic: 382.171498776
- Cas no. 143322-58-1

6.2.7 Structure

6.2.8 Description

Eletriptan is a second generation triptan drug (selective serotonin 5-HT1B/1D receptor agonist) for the treatment of migraine headaches.
6.2.9 Physical, chemical and biological properties

- **Dissociation Constant:** 6.8
- **Melting Point:** 168-173°C
- **Log P:** 3.9
- **Half–life:** The terminal elimination half-life of eletriptan is approximately 4 h.
- **Volume of Distribution:** Approx: 138 L
- **Clearance:** 3.9 L/h
- **Protein binding:** Plasma protein binding is moderate and approximately 85%.

6.2.10 Uses

Eletriptan is used for the treatment of migraine in adult patients known as serotonin agonists generally referred to as a triptan. Patients affected by migraine may experience a severely painful, throbbing headache, either on one or both sides of the head. Other symptoms include nausea, vomiting and sensitivity to light and sound. Certain patients may also notice flashing lights (called aura). The drug candidate aims to treat these symptoms by reducing the swelling of blood vessels in the brain, and by blocking the release of substances which can cause migraine symptoms.

6.2.11 Pharmacology

6.2.11.1 Mechanism of action

Eletriptan binds with high affinity to 5-HT$_{1B}$, 5-HT$_{1D}$ and 5-HT$_{1F}$ receptors, has modest affinity for 5-HT$_{1A}$, 5-HT$_{1E}$, 5-HT$_{2B}$ and 5-HT$_{7}$ receptors, and little or no affinity for 5-HT$_{2A}$, 5-HT$_{2C}$, 5-HT$_{3}$, 5-HT$_{4}$, 5-HT$_{5A}$ and 5-HT$_{6}$ receptors. At adrenergic alpha1, alpha2, or beta; dopaminergic D1 or D2; muscarinic; or opioid receptors Eletriptan shows no significant affinity or pharmacological activity [16]. Two theories have been projected to explain the efficacy of 5-HT receptor agonists in migraine. One theory suggests that activation of 5-HT1 receptors located on intracranial blood vessels, leads to vasoconstriction, which is correlated with the relief of migraine headache. The other
hypothesis suggests that activation of 5-HT1 receptors on sensory nerve endings in the trigeminal system results in the inhibition of pro-inflammatory neuropeptide release [17].

### 6.2.11.2 Pharmacodynamic

Eletriptan is a selective 5-hydroxytryptamine receptor agonist showing higher affinity for human recombinant 5-HT$_{1B}$, 5HT$_{1D}$, and 5HT$_{1F}$ receptor. In the study Eletriptan treated anesthetized dog have shown to reduce carotid arterial blood flow, with only a small increase in arterial blood pressure at high doses. While the effect on blood flow was selective for the carotid arterial bed, decreases in coronary artery diameter were observed. Eletriptan has also been shown to inhibit trigeminal nerve activity in the rat. In humans this receptor is responsible for the constriction of cephalic arteriovascular anastamoses. *In-vitro* studies have revealed that eletriptan were higly effective in producing contractile response in human isolated middle meningeal artery and saphenous veins. Eletriptans has been recorded for vasopressive activity on the systemic and pulmonary vascular beds. During the migraine attack drug absorption is delayed due to gastric stasis leading to the difference in the absorption kinetics of eletriptan. *In vivo* studies confirm the ability of eletriptan to cause vasoconstriction, eventhough the effect is not clinically significant [18].

The vascular effects of serotonin agonists have been studied to evaluate their potential for eliciting cardiovascular events, increasing blood pressure, and producing other hemodynamic effects. The ability of serotonin agonists to cause vasoconstriction has limited their usefulness in clinical practice, especially in patients with a cardiovascular history. Human histology has specified selectiveness for meningeal arteries than for coronary arteries compared with sumatriptan (63–86% for eletriptan vs 5–30% for sumatriptan), and it is also more selective for the cranial veins than the saphenous veins compared with sumatriptan (18–66% for eletriptan vs 5–25% for sumatriptan). *In vitro* data suggest that drug is more selective for the carotid and meningeal arteries than the peripheral arteries compared with sumatriptan, a feature that lowers its potential to reduce coronary blood flow [19].
6.2.11.3 Absorption and Distribution

Eletriptan is more lipophilic as compared to sumatriptan, suggesting the theoretical increased intestinal absorption, central nervous system penetration, and volumes of distribution (Vd 2.5 L/kg) of Eletriptan. Dose-ranging studies confirmed that the absolute oral bioavailability (50%), whereas peak plasma concentrations are reached in approximately 1 h, irrespective of the dose Eletriptan exhibits linear kinetics, as its peak plasma concentrations increase in a dose dependent manner. The drug protein binding upto 85% which is greater than the other triptans the difference have not been found to incur additional adverse effects or drug interactions [20].

6.2.11.4 Drug metabolism and pharmacokinetics

Due to the lipophilic nature of the drug absorption from the GI track is rapid after oral administration with an absolute bioavailability of about 50%. From the records it is revealed that the mean absorption time is about 1.5 hrs with the median of 2 hrs during the attack. The major enzyme involved is CYP3A4 which is responsible for metabolism. Central nervous system penetration by eletriptan is limited by an active. The N-demethyalated metabolite is the only known active metabolite of eletriptan which has plasma concentration ranging from 10 to 20 % of the parent drug. Central nervous system penetration by eletriptan is limited by an active P-glycoprotien blood brain barrier efflux system that has to overcome, in order to get adequate central penetration. plasma levels of other drugs are not affected as Eletriptan does not inhibit or induce any CYP enzymes. Following an iv. Eletriptan injection, linear pharmacokinetics is observed in healthy volunteers. Overall, eletriptan has rapid oral absorption, good bioavailability, a long half-life, and good penetration to the central nervous system because of its lipophilicity [21].

6.2.11.5 Excretion

Eletriptan is eliminated through hepatic metabolism with cytochrome P450 3A4 isoenzyme. Eletriptan has a long dose dependant half life of 4-5 h after oral administratin. Both the oral and intravenous dosage has the same half life of 4 h irrespective of their
doses. About 9% of the dose is found unchanged in the urine during the first 24 hrs after a single IV dose.

6.2.11.6 Tolerability

All the dose range of eletriptan were well tolerated fallowing either single or double dose. The most common adverse events were asthenia, dizziness, somnolence and nausea. A 40 mg dose was founded to be well tolerated in the efficacy study and safety of eletriptan in adolescents with the ages fro 12-17 years with migraine, with an adverse events profile similar to that in the Phase III trials in adult patients. Since eletriptan is extensively metabolized by the liver, patients with mild to moderately impaired hepatic function have a slight increase in systemic exposure to oral eletriptan [22].

6.2.11.7 Toxicity

Pharmacological data recorded suggest, the occurance of hypertension or other more serious cardiovascular symptoms with overdose, which includes coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation. Although these reactions are rare, they can be life threatening. As with other serotonin agonists, eletriptan has reportedly caused sensations of chest tightness, pain, pressure, and heaviness. In placebo-controlled trials, the overall rates of chest symptoms (tightness, pain, pressure) were 1%, 2%, and 4% for eletriptan 20, 40, and 80 mg, respectively indicating that the lower doses are more significant than the larger doses [23].

6.2.11.8 Dosage and Administration

The U.S. Food and Drug Administration has approved oral eletriptan 20 and 40 mg. A single oral dose of eletriptan 40 mg should be taken at the onset of migraine pain. If pain persists a single dose may be repeated after 2 h from initial dose. The maximum daily dose is 80 mg. The administration of eletriptan with high-fat meals increases its absorption by 20–30%. Patients with uncontrolled hypertension, coronary artery disease, or peripheral vascular disease should start with the lowest recommended dose of 20 mg because of a risk of increased blood pressure and vasospasm. Patients with severe hepatic
dysfunction should also start with the 20 mg dose because of a risk of drug accumulation and increased toxicity. Patients taking drugs that inhibit the CYP3A4 enzyme (e.g., ketoconazole, ritonavir, lovastatin) should not exceed the maximum daily dose of 40 mg. [24]

### 6.2.11.9 Clinical Studies

Clinical trials indicated that Eletriptan was well tolerated and safe across its dosing range of 20 mg to 80 mg. The adverse event profile of eletriptan 20 mg was similar to placebo, while the most commonly used dose, eletriptan 40 mg, has an adverse event profile that is only marginally higher than placebo. Eletriptan was safe and well tolerated regardless of age or gender and for both short and long-term treatment. The margin of cardiovascular safety for Eletriptan was also confirmed by a well tolerated clinical study in which intravenous eletriptan in excess of an 80 mg dose was rapidly infused in patients undergoing coronary angiography. The triptan class in general is contraindicated in the patients with the symptoms or findings consistent with ischemic heart disease or other significant underlying cardiovascular disease. Eletriptan is metabolized primarily by the CYP3A4 enzyme. Because of its high margin safety, use of eletriptan is not recommended within at least 72 h of treatment with a limited list of 7 potent CYP3A4 inhibitors: Ketoconazole, Itraconazole, Nelfazodone, Troleandomycin, Clarithromycin, Ritonavir, and Nelfinavir [22, 25].

In the Clinical records, investigators assessed sustained headache responses, defined as headache response within 2 h without recurrence and no use of rescue drug or second dose of study drug. Patients receiving eletriptan 20, 40, or 80 mg achieved sustained headache response rates (29%, 39%, and 42%, respectively) significantly higher than that of placebo (10%, p<0.0001). Eletriptan 20, 40, and 80 mg also significantly improved functional responses at 2 h (51%, 60%, and 57%, respectively) compared with placebo (26%, p<0.001). In addition, eletriptan 20, 40, and 80 mg significantly reduced rates of nausea, photophobia, and phonophobia at 2 h (41%, 53%, and 44%, respectively) compared with placebo (24%, p < 0.001). The well-designed study demonstrated that eletriptan 20, 40, and 80 mg were statistically and clinically significantly superior to placebo in terms of 2 h headache response, pain-free response,
reduction in functional impairment, and relief of migraine-associated symptoms. There was no evidence to note the clinical difference in headache recurrence rates. In the study, finding was that eletriptan 40 and 80 mg did not significantly differ in 2 h headache or pain-free response rates. Dose response relationship was observed in contrast to results of other studies of eletriptan. [23, 26]
6.3 Zolmitriptan (ZMT)

6.3.1 Drug class: Antimigraine.

6.3.2 Proprietary Name: Zomig.

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

6.3.4 Formula: C_{16}H_{21}N_{3}O_{2}.

6.3.5 Category: Serotonin antagonists, serotonin 5-HT1 Receptor agonists, serotonin receptor antagonist, anti-migraine agents.

6.3.6 Molecular Weight and CAS number:
- Average: 287.3568
- Monoisotopic: 287.163376931
- CAS number: 139264-17-8

6.3.7 Structure:

6.3.8 Description

ZMT is a synthetic tryptamine derivative and appears as a white powder that is readily soluble in water. This compound belongs to the class of organic compounds known as tryptamines and derivatives. These are compounds containing the tryptamine backbone, which is structurally characterized by an indole ring substituted at the 3-position by an ethanamine.
6.3.9 Physical chemical and biological properties

- **Dissociation Constant:**
  - $P_{ka}$ strong acid - 13
  - $P_{ka}$ strong base - 9.55
- **$\text{Log P}$:** 1.6
- **Melting point:** 136-141 °C
- **Bioavailability:** Mean absolute oral bioavailability is approximately 40%. Food has no affect on the rate and extent of absorption.
- **Half–life:** The mean elimination half-life of zolmitriptan and of the active N-desmethyl metabolite is 3 h.
- **Protein binding:** 25%
- **Volume of Distribution:** 8.4 ± 3.3 L/k
- **Clearance:** 25.9 mL/min/k

6.3.10 Pharmacology

6.3.10.1 Mechanism of action

ZMT binds with high affinity to human 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors leading to cranial blood vessel constriction. Theoretically migraine headache occurs due to local cranial vasodilatation and tend to release of sensory neuropeptides such as vasoactive intestinal peptide, substance P and calcitonin gene-related peptide through nerve endings in the trigeminal system. The therapeutic activity of ZMT for the treatment of migraine headache is endorsed to the agonist effects at the 5HT$_{1B/1D}$ receptors on intracranial blood vessels and sensory nerves of the trigeminal system resulting in cranial vessel constriction and inhibition of pro-inflammatory neuropeptide release [27].

6.3.10.2 Pharmacodynamics

Zolmitriptan is a selective agonist of serotonin 5-HT type 1B and 1D receptors. It is structurally and pharmacologically related to other selective 5-HT$_{1B/1D}$ receptor agonists, and has only a weak affinity for 5-HT$_{1A}$, 5-HT$_{5A}$, and 5-HT$_{7}$ receptors and no
significant affinity or pharmacological activity at 5-HT_2, 5-HT_3 or 5-HT_4 receptor subtypes or at alpha1-, alpha2-, or beta-adrenergic, dopamine1,; dopamine2; muscarinic, or benzodiazepine receptors. Drugs used in the acute treatment of migraine are well known to cause constriction of cranial blood vessels and a redistribution of blood flow in the cranial circulation. It can be correlated to humans with the relief of migraine headache. ZMT is also known to trigger 5-HT_1 receptors on peripheral terminals of the trigeminal nerve innervating cranial blood vessels, leading to the antimigrainous effect of ZMT in humans. Reductions in carotid arterial conductance with ZMT are almost exclusively caused by constriction of cranial arteriovenous anastomotic shunts. Interestingly ZMT produces no change in intracranial cerebral blood flow. From the animal studies it has been confirmed that ZMT has the ability to inhibit trigeminovascular activation both peripherally and centrally, actions which may be relevant to its therapeutic efficacy.

Even though increase in blood pressure in healthy volunteers, is reported by the single doses of ZMT 1 to 50 mg, changes are generally not considered to be clinically significant and individual data often showed high variability. ZMT 20 mg does not significantly alter cardiac output or heart rate in healthy volunteers. Data obtained from volunteers and patients with migraine shows that ZMT acts centrally on serotonergic pathways indicating that the drug does not induce cognitive or psychomotor impairment in healthy volunteers [28-30].

6.3.10.3 Absorption and Distribution

After oral administration ZMT is rapidly absorbed in healthy volunteers with 75% of the maximum plasma concentration (C_{max}) 1 h. However, there was considerable interindividual variation in plasma ZMT concentrations a single 2.5 mg dose, individual C_{max} and AUC values ranged from 1.3 to 6.7 μg/L and 6.4 to 38.9 μg/L at every h, respectively. The mean absolute bioavailability of oral ZMT 2.5 mg in 20 healthy volunteers was calculated by reference to an intravenous dose giving a similar AUC value, was 39% which was lower than the 49% obtained with a 10mg dose and compares with a value of 14% for therapeutic doses of sumatriptan.
The absorption of ZMT 10 mg is delayed during migraine associated with severe headache, nausea and photophobia. Area under the plasma concentration versus time curve (AUC) and $C_{\text{max}}$ values showed approximate dose proportionality over the range ZMT 2.5 to 50 mg. It has also been reported that food has no significant effect on the oral absorption of a 5mg dose of ZMT. When the drug was coadministered with a standard breakfast, $C_{\text{max}}$ and AUC values obtained were 87 and 84 % of compared to those drug administered in the fasting state. The mean absolute bioavailability of oral ZMT 2.5 mg in healthy volunteers is 39% whereas the binding to plasma proteins is 25%. Mean volume of distribution following oral 2.5 and 5 mg doses of ZMT is reported to be 8.3 L/kg [29, 31].

### 6.3.10.4 Metabolism and Elimination

ZMT is reported to have 3 major metabolites: an active $N$-desmethyl, an $N$-oxide and an indole acetic acid metabolite. ZMT is rapidly eliminated from the body. In-vitro studies conducted in human hepatocytes and microsomes and drug interaction studies indicate that the drug is metabolised by the cytochrome P450 isoenzyme (CYP) 1A2 and by monoamine oxidase A. ZMT is cleared principally by hepatic metabolism followed by urinary excretion of its metabolites. Metabolism of the $N$-desmethyl metabolite occurs via monoamine oxidase A. The mean plasma elimination half-life ($t_{1/2}$) is about 2.6 h after a single 2.5 or 5 mg dose. Oral bioavailability and mean $C_{\text{max}}$ and AUC values are generally higher in women than in men, with the significant difference with doses ≥ 5 mg, although $t_{1/2}$ is similar.

Dosage adjustments are not necessarily reduced in the elderly population with renal clearance of ZMT and its active metabolite. Patients with hepatic impairment have increased systemic exposure to ZMT. Patients with moderate or severe hepatic impairment are recorded with prolonged $t_{1/2}$ and reduced apparent total clearance when compared with healthy volunteers. Hence, it is recommended that the dose should be reduced in patients with moderate or severe hepatic impairment. In a trial in 6 volunteers, almost all (91.5%) of a radiolabelled 25mg dose of ZMT was eliminated from the body within 7 days [28, 32, 33].
6.3.10.5 Clinical Efficacy

Most clinical trials assessed the effects of ZMT treatment on a single acute migraine attack of moderate or severe intensity and were randomised, placebo-controlled, double-blind and parallel group in design which involved large number of adults with moderate to severe migraine. Patients selected were in between the age of 18 and 65 years and were required to have a diagnosis of migraine with or without aura satisfying the regulations implemented by International Classification Committee [34]. Secondary end-points Headache response was evaluated for 1 and 4 h after drug administration. A number of other secondary end-points were less consistently measured including pain-free response, recurrence of headache evaluating moderate to severe pain within 24 h of administration, complete response, use of liberate medication, effect on daily living, also included the improvement in related symptom to migraine viz: nausea, photophobia and phonophobia and effective migraine relief [35].

Doses of 2.5 and 5mg, was reported with rapid onset of action with significant headache relief at 45 minutes. After 2 h of drug administration headache response rates for the primary efficacy parameter of most migraine trials, for ZMT 2.5 and 5 mg ranged among 59 and 67% and were significantly greater than administered placebo (15 to 36 %). ZMT 2.5 and 5 mg versus placebo showed the increased pain-free response. A single dose of ZMT 2.5 to 25 mg is consistently significantly more effective than placebo in relieving single episodes of migraine headache of moderate to severe intensity as measured using a number of end-points, when given within 12 h of migraine onset. The efficacy of the drug was maintained even after repeated dose administration while the efficacy of the drug was reported to sustain for 24 h in most of the patient and persisted for almost a year, whereas high headache response rates was reported over the attacks in nonblinded studies [36].

The efficacy of the drug doesn’t basically depend on the timing of administration with regard to migraine onset within 4 h versus > 4 h of onset while the drug was effective in patients who awake with a migraine headache. Clinical data suggest effectiveness of the drug in the treatment of migraine coupled with menses and migraine with aura. With ZMT treatment nausea, photophobia and phonophobia which are basically associated with migraine are improved considerably. ZMT 5 mg showed
parallel efficacy to sumatriptan 100 mg when used to treat a single attack (for headache relief). When given for acute treatment of multiple attacks in single trials, ZMT proved to be more effective than sumatriptan 25 and 50 mg whereas no tachyphylaxis was reported with headache and pain free response.

Headache response at 2 h indicates that ZMT 2.5 mg was significantly more effective than sumatriptan 25 or 50 mg. Severe or moderate intensity headache persisted at 4 h is more common with placebo than ZMT. Very few recipients of ZMT than placebo experience headache recurrence. Complete response rates for 2-24 h also indicate that ZMT 2.5 and 5 mg is superior to placebo and ZMT 5mg has similar efficacy to sumatriptan 100 mg [28, 37].

6.3.10.5 Tolerability

Data generated from the clinical trials from the population of more than 2000 volunteers and the collective data of 2750 patients for tolerability after receiving the drug (1 to 25 mg) trials indicated tolerance effect of the drug. Less than 1% of patients with adverse event were dose dependent across the range 1 to 15 mg. The most general adverse events identified of the drug with the dose was asthenia, heaviness (other than chest), dry mouth, nausea, dizziness, somnolence, paraesthesia, warm sensation, tightness, vasodilation and chest pain. Adverse events addressed were normally of mild or moderate intensity, temporary and were rectified without involvement or withdrawing the treatment. Single doses of ZMT 1 to 25 mg reported no any clinically significant change on mean systolic or diastolic blood pressure or heart rate in patients with migraine. Data generated from the pooled tolerability data suggest that the incidence of chest-related adverse events with ZMT 2.5 to 10 mg was low and these symptoms were generally mild, momentary and not so serious. With ZMT 1 to 20 mg the incidence of ECG obtained was similar to that with placebo.

ZMT didn’t show any clinically significant change in clinical chemistry, hematology or urinalysis. The adverse event profiles of oral ZMT 5mg and sumatriptan 100 mg were very similar in a placebo-controlled comparative studies. Naratriptan 2.5 mg emerge to be tolerate better than ZMT 2.5 mg in the only trial to compare these agents, although this trial was not completed and it was reported that no statistical
analysis was performed. The most regular adverse events were asthenia, tightness, dry mouth, nausea, dizziness, paraesthesia and somnolence. 4.7 and 8% of patients withdrew from ZMT treatment because of adverse events in 2 long term studies [38, 39].

6.3.10.6 Drug Interactions

Clinically assessed data of drug interactions were studied for various interactions and the possible drug being supplied during the treatment. The agents most commonly coadministered along with ZMT includes ergot derivatives with or without caffeine; paracetamol (acetaminophen), propranolol and pizotifen. There were no major interactions identified in the clinical data. Even though there was no any significant interaction between drug and ergot derivatives, these agents are recommended to avoid the administration together or within 24 h of each other.

Administration of drug with inhibitors of CYP1A2 and/or monoamine oxidase (MAO)-A reduces the clearance of ZMT. In the study conducted for treatment with dihydroergotamine 5 mg/day for 10 days indicated no any significant change clinically, although insignificant increase in blood pressure was observed following a single dose of ZMT 10mg. When ergotamine/caffeine or dihydroergotamine coadministered with ZMT didn’t reported any alteration in the pharmacokinetic profile of drug. There was a small, clinically insignificant reduction in the rate and extent of paracetamol (acetaminophen) absorption when ZMT 10mg given in combination with paracetamol 1g in 15 healthy volunteers. The reports generated showed that paracetamol $C_{\text{max}}$ and AUC was marginally increased, whereas ZMT $C_{\text{max}}$ and AUC values (11%) reduced the renal clearance by 9% ZMT. Eight days of treatment with pizotifen 1.5 mg/day showed very little or no any clinically insignificant effects on the pharmacokinetics of a single ZMT 10 mg dose in 12 healthy volunteers.

Administration of ZMT with inhibitors of CYP1A2 and/or MAO-A reduced the clearance of ZMT in healthy volunteers and ZMT dose reductions are suggested when these drugs are given concomitantly For example, moclobemide, an inhibitor of MAO-A slightly reduced the clearance of ZMT and significantly increased the AUC of the $N$-desmethyl metabolite [38,40].
CHAPTER 6

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6.3.10.7 Dosage and Administration

The initial dose of ZMT is 2.5 mg is recommended. Higher doses (5 mg) of ZMT have showed additional clinical benefits. Based on the efficacy and tolerability studies ZMT 2.5 mg emerge to be the most suitable dose. Dose is repeated after 2 h when headache is reoccurred, but should not exceed a total of 10 mg within a 24 h period. Considering the hepatic impairment from patients with moderate to severe, dosage recommendation vary among countries.

In the clinical data obtained indicated that ZMT is avoided in patients with ischaemic heart disease, coronary artery vasospasm or uncontrolled hypertension, as the selective 5-HT\textsubscript{1B} receptor agonists as a class have been associated with coronary vasospasm. As the clearance of ZMT is reduced after 24 h the maximum dose of the selective 5-HT\textsubscript{1B/1D} receptor agonist should not exceed 5 mg to the patients receiving MAOI. Patients receiving parallel treatment with ZMT and SSRIs should be monitored for weakness, hyperreflexia and in coordination that have been reported [28, 41].
6.4 References


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