ZOMIG RAPIMELT 2.5 mg Tablets
ASTRAZENECA

Presentation
Zomig Rapimelt is presented as orodispersible tablets containing 2.5 mg of zolmitriptan.

Indications
Zomig Rapimelt is indicated for the acute treatment of migraine with or without aura.

Dosage and method of administration
The recommended dose of Zomig Rapimelt to treat a migraine attack is 2.5 mg.

The Zomig Rapimelt orodispersible tablet rapidly dissolves when placed on the tongue and is swallowed with the patient’s saliva. A drink of water is not required when taking the Zomig Rapimelt orodispersible tablet. Zomig Rapimelt orodispersible tablets can be taken when water is not available thus allowing early administration of treatment for a migraine attack. This formulation may also be beneficial for patients who suffer from nausea and are unable to drink during a migraine attack, or for patients who do not like swallowing conventional tablets.

If symptoms persist or return within 24 hours, a second dose has been shown to be effective. 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 Zomig Rapimelt. Significant efficacy is apparent within 1 hour of dosing.

Zomig Rapimelt is equally effective whenever taken during a migraine attack; although it is advisable that Zomig Rapimelt 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 Zomig Rapimelt, in a 24 hour period, should not exceed 10 mg.

Zomig Rapimelt is not indicated for prophylaxis of migraine.

Use in Patient Subgroups
Zomig Rapimelt is consistently effective in migraine, with or without aura, and in menstrually associated migraine. The efficacy of Zomig Rapimelt is also unaffected by gender, age (see use in Children and Elderly below), duration of the attack, pre-treatment nausea and concomitant use of common prophylactic migraine drugs.

Use in Children
Safety and efficacy of Zomig Rapimelt in paediatric patients have not been established.

Use in the Elderly
The safety and efficacy of Zomig Rapimelt in individuals aged over 65 years have not been systematically evaluated.

Patients with Hepatic Impairment
Although metabolism is reduced in patients with mild or moderate hepatic impairment (see Pharmacokinetic Properties Section), no dosage adjustment is required. However, for patients with severe hepatic impairment a maximum dose of 5 mg in 24 hours is recommended.

Patients with Renal Impairment
No dosage adjustment required (see Pharmacokinetic Properties Section).

Contraindications
Zomig Rapimelt is contraindicated in patients with:
• Known hypersensitivity to any component of the product.
• Uncontrolled hypertension.
• Ischaemic heart disease.
• Coronary vasospasm/Prinzmetal’s angina.
• A history of cerebrovascular accident (CVA) or transient ischaemic attack (TIA).
• Concomitant administration of Zomig Rapimelt with ergotamine or ergotamine derivatives or other 5-HT1 receptor agonists.

Warnings and precautions for use
Zomig Rapimelt should only be used where 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 Zomig Rapimelt 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 5HT1B/1D agonists.

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

In very rare cases, this class of compounds (5HT1B/1D agonists), has been associated with coronary vasospasm, angina pectoris and myocardial infarction. In patients with risk factors for ischaemic heart disease, cardiovascular evaluation prior to commencement of treatment with this class of compounds, including Zomig Rapimelt, is recommended (see Contraindications Section). 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 5HT1B/1D agonists, atypical sensations over the precordium (see Possible Adverse Reactions Section) have been reported after the administration of zolmitriptan.

If chest pain or symptoms consistent with ischaemic heart disease occur, no further doses of zolmitriptan should be taken until after appropriate medical evaluation has been carried out.

As with other 5HT1B/1D agonists, transient increases in systemic blood pressure 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.

As with other 5HT1B/1D agonists, there have been rare reports of anaphylaxis/anaphylactoid reactions in patients receiving Zomig.

Excessive use of an acute anti-migraine medicinal product may lead to an increased frequency of headache, potentially requiring withdrawal of treatment.

Patients with phenylketonuria should be informed that Zomig Rapimelt orodispersible tablets contain phenylalanine (a component of aspartame). Each 2.5 mg orodispersible tablet contains 2.81 mg of phenylalanine.

**Interactions with other medicaments and other forms of interactions**

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

The pharmacokinetics and tolerability of Zomig Rapimelt were unaffected by acute symptomatic treatments such as paracetamol, metoclopramide and ergotamine. Concomitant administration of other 5HT1B/1D agonists within 12 hours of Zomig Rapimelt treatment, should be avoided.

Data from healthy subjects suggest there are no pharmacokinetic or clinically significant interactions between Zomig and ergotamine, however, the increased risk of coronary vasospasm is a theoretical possibility. Therefore, it is advised to wait at least 24 hours following the use of ergotamine containing preparations before administering Zomig. Conversely it is advised to wait at least six hours following use of Zomig before administering any ergotamine preparation (see Contraindications).

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 Zomig Rapimelt in 24 hours is recommended in patients taking a MAO-A inhibitor.

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 Zomig Rapimelt 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 (eg ciprofloxacin).
Following the administration of rifampicin, no clinically relevant differences in the pharmacokinetics of zolmitriptan or its active metabolite were observed. As with other 5HT1B/1D agonists, there is the potential for dynamic interactions with the herbal remedy St John’s Wort (Hypericum perforatum) which may result in an increase in undesirable effects.

**Pregnancy and lactation**

**Pregnancy**

Zomig Rapimelt should be used in pregnancy only if the benefits to the mother justify potential risk to the foetus. There are no studies in pregnant women, but there is no evidence of teratogenicity in animal studies.

**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 Zomig Rapimelt to women who are breast-feeding.

**Effects on ability to drive and use machines**

There was no significant impairment of performance of psychomotor tests with doses up to 20 mg Zomig Rapimelt. Use is unlikely to result in an impairment of the ability of patients to drive or operate machinery. However it should be taken into account that somnolence may occur.

**Possible adverse reactions**

Zomig Rapimelt is well tolerated. Adverse reactions are typically mild/moderate, transient, not serious and resolve spontaneously without additional treatment. Possible adverse reactions tend to occur within 4 hours of dosing and are no more frequent following repeated dosing.

The incidences of ADRs associated with Zomig therapy are tabulated below according to the format recommended by the Council for International Organizations of Medical Sciences (CIOMS III Working Group; 1995).

<table>
<thead>
<tr>
<th>Frequency</th>
<th>System Organ Class</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common (≥10%)</td>
<td>Gastrointestinal Disorders</td>
<td>- None</td>
</tr>
<tr>
<td>Common (≥1% and &lt; 10%)</td>
<td>Gastrointestinal Disorders</td>
<td>Dry Mouth, Nausea</td>
</tr>
<tr>
<td></td>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td>Muscle weakness, Myalgia</td>
</tr>
<tr>
<td></td>
<td>Nervous System Disorders</td>
<td>Abnormalities or disturbances of sensation, Asthenia, Dizziness, Dysaesthesia, Heaviness, tightness, pain or pressure in throat, neck, limbs or chest (with no evidence of ischaemic changes on ECG), Paraesthesia, Somnolence, Warm sensation</td>
</tr>
<tr>
<td>Rare (≥0.01% - &lt;0.1%)</td>
<td>Cardiac Disorders</td>
<td>Palpitations, Tachycardia</td>
</tr>
<tr>
<td></td>
<td>Immune System Disorders</td>
<td>Anaphylaxis, Anaphylactoid Reactions, Hypersensitivity reactions</td>
</tr>
<tr>
<td></td>
<td>Nervous System Disorders</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>Angioedema, Urticaria</td>
</tr>
<tr>
<td>Very rare (&lt;0.01%)</td>
<td>Cardiac Disorders</td>
<td>Angina pectoris, Coronary Vasospasm, Myocardial Infarction</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal Disorders</td>
<td>Abdominal pain, Bloody diarrhoea, Gastrointestinal infarction or necrosis, Gastrointestinal ischaemic events, Ischaemic colitis, Splenic Infarction</td>
</tr>
<tr>
<td>Very rare (&lt;0.01%)</td>
<td>Renal and Urinary Disorders</td>
<td>Polyuria, Urinary frequency, Urinary urgency</td>
</tr>
<tr>
<td></td>
<td>Vascular Disorders</td>
<td>Transient increases in systemic blood pressure very rarely associated with significant clinical events</td>
</tr>
</tbody>
</table>

1. As with other 5HT1B/1D agonists, there have been rare reports of hypersensitivity reactions, including anaphylaxis/anaphylactoid reactions, urticaria and angioedema.
2. As with other acute migraine treatments, including 5HT1B/1D agonists, there have been rare reports of headache.
3. In very rare cases, as with other 5HT1B/1D agonists, angina pectoris, myocardial infarction have been reported.
4. As with other 5HT1B/1D agonists, very rare reports of gastrointestinal ischaemic events including ischaemic colitis, gastrointestinal infarction or necrosis, which may present as bloody diarrhoea or abdominal pain, have been received.
5. As with other 5HT1B/1D agonists, transient increases in systemic blood pressure, very rarely associated with significant clinical events, have been reported.
In addition to these peripheral actions, 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. Zolmitriptan blocks this reflex pathway and the release of VIP.

**Pharmacokinetic Properties**

Following oral administration of Zomig conventional tablets, zolmitriptan is rapidly and well absorbed (at least 64%). The mean absolute bioavailability of the parent compound is approximately 40%. There is an active metabolite (183C91, the N-desmethyl metabolite) which is also a 5HT1B/1D agonist and is 2 to 6 times as potent, in animal models, as zolmitriptan. The Zomig Rapimelt orodispersible formulation was found to be bioequivalent with the conventional tablet in terms of AUC and Cmax for zolmitriptan and its active metabolite (183C91). The time to maximum plasma concentration following administration of Zomig Rapimelt orodispersible is similar for the active metabolite (183C91) but can be prolonged for zolmitriptan with this formulation relative to the conventional tablet. In a clinical pharmacology study to compare the two formulations, for the active metabolite 183C91, the tmax ranged from 0.75 to 5 hours (median 3.0 hours) for the conventional tablet, and 1 to 6 hours (median 3.0 hours) for the orodispersible tablet, whereas for zolmitriptan the ranges were 0.5 to 3 hours (median 1.5 hours) and 0.6 to 5 hours (median 3.0 hours), respectively. However, plasma concentrations of zolmitriptan for the orodispersible and conventional tablet formulations are similar up to 45 minutes post dose, the period of most importance for initial absorption following administration. Zolmitriptan is eliminated largely by hepatic bio-transformation 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.
Concomitant administration of Zomig with ergotamine/caffeine was well tolerated and did not result in any increase in adverse events or blood pressure changes as compared to Zomig alone.

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.

**Pharmaceutical Particulars**

**Instructions for use/handling**
Zomig Rapimelt orodispersible tablets: The blister pack should be peeled open as shown on the foil (tablets should not be pushed through the foil). The Zomig Rapimelt tablet should be placed on the tongue, where it will dissolve and be swallowed with the saliva.

**Storage**
Do not store above 30oC.

**Shelf life**
Please refer to expiry date on the blister strip or outer carton.

**Pack size**
Please refer to the outer carton for pack size.

**Date of revision of the text**
September 2004

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 of Zomig. 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 Cmax 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 Cmax were reduced by 33% and 44% 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, of which one third is renal clearance.

Renal clearance is greater than glomerular filtration rate suggesting renal tubular secretion. The volume of distribution following iv administration is 2.4 L/kg. Plasma protein binding 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 (7-8 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.