Package Insert for ZOLMIFOR ODT

SCHEDULING STATUS
S4

PROPRIETARY NAME AND DOSAGE FORM
ZOLMIFOR ODT orodispersible tablets

COMPOSITION
Active ingredient:
Each orodispersible tablet contains 2,5 mg zolmitriptan.

Inactive ingredients:
Aspartame (NutraSweet), basic butylated methacrylate copolymer, low substituted hydroxypropyl cellulose, magnesium aluminometasilicate, magnesium stearate, mannitol, peppermint flavour, silica colloidal anhydrous, sodium laurilsulfate and talc.

Contains artificial sweetener (aspartame).

Sugar free.

PHARMACOLOGICAL CLASSIFICATION
A 7.3 Migraine preparations

PHARMACOLOGICAL ACTION
Pharmacodynamic properties:
Zolmitriptan is a selective agonist for the vascular human recombinant 5-H_{1B} and 5-HT_{1D} receptor subtypes. Zolmitriptan is a high affinity 5-$HT_{1B/1D}$ receptor agonist with modest affinity for 5-HT_{1A} receptors. Zolmitriptan has no significant affinity (as measured by radioligand binding assays) or pharmacological activity at 5-HT_1, 5-HT_2, 5-HT_3, alpha$_1$, alpha$_2$, or beta$_1$, adrenergic; H_1, H_2, histaminic; muscarinic; dopaminergic$_1$ or dopaminergic$_2$ receptors. The 5-HT_{1D} receptor is predominately located presynaptically at both the peripheral and central synapses of the trigeminal nerve.

In acute migraine, vasodilatation occurs with the activation of a reflex pathway mediated by trigeminal orthodromic fibres and parasympathetic innervation of the cerebral circulation via the release of vasoactive intestinal peptide (VIP) as a main effector transmitter. Zolmitriptan blocks this reflex pathway and the release of VIP.

Pharmacokinetic properties:
Absorption:
The mean absolute bioavailability of the parent compound is approximately 40 %.
In healthy patients, 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. The zolmitriptan orodispersible formulation has similar AUC and C_{max} compared to the conventional formulation; but there is a significant delay in T_{max} when compared to the conventional formulation, however there is no evidence that the delay in T_{max} causes a delay in the onset of efficacy.

Elimination:
Zolmitriptan is eliminated largely by hepatic biotransformation followed by urinary excretion of the metabolites. There are 3 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 active metabolites are approximately half those of the parent medicine. Over 60 % of a single oral dose is excreted in the urine (mainly as the indole acetic acid metabolite) and about 30 % in faeces, mainly as unchanged parent compound.

Renal clearance is greater than glomerular filtration rate suggesting renal tubular secretion. 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.

Special populations:
Hepatic impairment:
The AUC and C_{max} are 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, is decreased. For the *N*-desmethyl zolmitriptan 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.

Renal impairment:
Renal clearance of zolmitriptan and all 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.

The elderly:
The pharmacokinetics of zolmitriptan in healthy elderly patients are similar to those in healthy young volunteers.

INDICATIONS
ZOLMIFOR ODT is indicated for the acute treatment of migraine with or without aura in adults.

CONTRAINDICATIONS
- **ZOLMIFOR ODT** is contraindicated in patients with known hypersensitivity to zolmitriptan or to any components of **ZOLMIFOR ODT** (see **COMPOSITION**).
- **ZOLMIFOR ODT** must not be given to patients with severe hypertension.
- Ischaemic heart disease.
- Coronary vasospasm / Prinzmetal's angina.
- Moderate to severe hepatic impairment.
- A history of cerebrovascular accident (CVA) or transient ischaemic attack (TIA).
- Concomitant administration of **ZOLMIFOR ODT** with ergotamine or its derivatives, or other 5-HT_1 receptor antagonists.
- **ZOLMIFOR ODT** should not be given to patients with symptomatic Wolff-Parkinson-White syndrome or dysrhythmias associated with other cardiac accessory conduction pathways.

WARNINGS AND SPECIAL PRECAUTIONS
Migraineurs may be at risk of certain cerebrovascular events. Cerebral haemorrhage, subarachnoid haemorrhage, stroke and other cerebrovascular events have been reported in patients treated with **ZOLMIFOR ODT**.

ZOLMIFOR ODT 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 **ZOLMIFOR ODT**, is recommended (see **CONTRAINDICATIONS**). These evaluations, however, may not identify every patient who has cardiac disease and serious cardiac events have occurred in patients without underlying cardiovascular disease.

Atypical sensations over the precordium have been reported after the administration of **ZOLMIFOR ODT**. Where such symptoms are thought to indicate ischaemic heart disease, no further doses of **ZOLMIFOR ODT** should be given and appropriate evaluation carried out.

ZOLMIFOR ODT 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 **ZOLMIFOR ODT** in hemiplegic or basilar migraine.

Excessive use of **ZOLMIFOR ODT** may lead to an increased frequency of headache, potentially requiring withdrawal of treatment.

Patients with phenylketonuria should be informed that **ZOLMIFOR ODT** orodispersible tablets contain phenylalanine (a component of aspartame).

Serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) has been reported following concomitant treatment with triptans and selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs). These reactions can be severe. If concomitant treatment with zolmitriptan (as in **ZOLMIFOR ODT**) and an SSRI or SNRI is clinically warranted, appropriate observation of the patient is advised, particularly during treatment initiation, with dose increases, or with addition of another serotonergic medication (see **INTERACTIONS**).

Use in patients over 65 years of age:
Safety and efficacy of **ZOLMIFOR ODT** in individuals aged over 65 years have not been systematically evaluated.

Patients with hepatic impairment:
Although zolmitriptan metabolism is reduced in patients with hepatic impairment, no dosage adjustment is required for patients with mild hepatic impairment. A maximum dose of 5 mg of **ZOLMIFOR ODT** in 24 hours is recommended.

Patients with renal impairment:
No dosage adjustment required.

Effects on ability to drive and use machines:
It should be taken into account that somnolence may occur (see **SIDE EFFECTS**).

INTERACTIONS
Concomitant administration of other 5-$HT_{1B/1D}$ agonists within 12 hours of **ZOLMIFOR ODT** treatment should be avoided.

There is also a potential for interactions with St John's wort (*Hypericum perforatum*), which may result in undesirable effects.

Ergot-containing medicines have been reported to cause prolonged vasospastic reactions (see **CONTRAINDICATIONS**). Because there is a theoretical basis that these effects may be additive, 24 hours should elapse between the use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and **ZOLMIFOR ODT**. Conversely, it is advised to wait at least 6 hours following the use of **ZOLMIFOR ODT** before administering an ergotamine-containing preparation.

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

The pharmacokinetics and tolerability of **ZOLMIFOR ODT** were unaffected by acute symptomatic treatments such as paracetamol, metoclopramide and ergotamine.

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

Following administration of moclobemide, an MAO inhibitor, there is an increase (26 %) in AUC for zolmitriptan (as in **ZOLMIFOR ODT**) and a 3-fold increase in AUC of the active metabolite. Therefore, a maximum intake of 5 mg **ZOLMIFOR ODT** in 24 hours is recommended in patients taking an MAO inhibitor.

Following the administration of cimetidine, a general P450 inhibitor, the half-lives of zolmitriptan and the active metabolite were significantly increased. A maximum dose of 5 mg **ZOLMIFOR ODT** 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.

PREGNANCY AND LACTATION
Safety in pregnancy and lactation has not been established.

ZOLMIFOR ODT is not recommended for women who are breastfeeding.

DOSAGE AND DIRECTIONS FOR USE
The recommended dose of **ZOLMIFOR ODT** to treat a migraine attack is 2,5 mg.

If a patient does not achieve satisfactory relief with 2,5 mg doses, subsequent attacks can be treated with 5 mg doses of **ZOLMIFOR ODT**.

ZOLMIFOR ODT is effective whenever the tablets are taken during a migraine attack; although it is advisable that the **ZOLMIFOR ODT** orodispersible tablets are taken as early as possible after the onset of migraine headache.

ZOLMIFOR ODT is an orodispersible tablet and can be taken when water is not available, or by patients who suffer from nausea and are unable to drink during a migraine attack.

The blister pack should be peeled open as shown on the foil (tablets should not be pushed through the foil). **ZOLMIFOR ODT** should be placed on the tongue, where it will dissolve and be swallowed with the saliva.

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.

In those patients who respond, statistically significant efficacy is apparent within 1 hour of dosing.

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

ZOLMIFOR ODT is not indicated for prophylaxis of migraine.

Use in patient subgroups:
Use in adolescents and children (under 18 years):
Safety and efficacy have not been established. Use of **ZOLMIFOR ODT** in adolescents and children is therefore not recommended. The efficacy and safety of **ZOLMIFOR ODT** in paediatric patients below 12 years have not been evaluated.

SIDE EFFECTS

Immune system disorders:	
Less frequent:	anaphylactoid reactions, hypersensitivity reactions, angioedema
Nervous system disorders:	
Frequent:	abnormalities or disturbances of sensation, dizziness, paraesthesia, somnolence, warm sensation, headache
Cardiac disorders:	
Frequent:	palpitations
Less frequent:	tachycardia, angina pectoris, coronary vasospasm, myocardial infarction
Vascular disorders:	
Less frequent:	transient increases in systemic blood pressure
Respiratory, thoracic and mediastinal disorders:	
Frequent:	dyspnoea
Gastrointestinal disorders:	
Frequent:	dry mouth, nausea, vomiting, dysphagia, dyspepsia, abdominal pain
Less frequent:	bloody diarrhoea, gastrointestinal infarction or necrosis, gastrointestinal ischaemic events, ischaemic colitis, splenic infarction
Skin and subcutaneous tissue disorders:	
Less frequent:	urticaria
Musculoskeletal, connective tissue and bone disorders:	
Frequent:	muscle weakness, myalgia
Renal and urinary disorders:	
Less frequent:	polyuria, increased urinary frequency, urinary urgency
General disorders and administrative site conditions:	
Frequent:	asthenia, heaviness, tightness, pain or pressure in throat, neck, limbs or chest.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
(See **SIDE EFFECTS** and **WARNINGS AND SPECIAL PRECAUTIONS**.)

Symptoms of overdose:
Sedation may be expected.

Treatment of overdose:
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.

The elimination half-life of zolmitriptan administration is approximately 3 hours and therefore monitoring of patients after overdose with **ZOLMIFOR ODT** orodispersible tablets should continue for at least 15 hours or while symptoms or signs persist.

IDENTIFICATION
White to off-white, round shaped, flat face bevelled edge tablets, debossed with '2.5' on one side and having a characteristic peppermint flavour.

PRESENTATION
ZOLMIFOR ODT is packed into Alu/Alu blister strips and placed in an outer carton; each carton contains 6 tablets.

STORAGE INSTRUCTIONS
Store at or below 25 °C.
Keep blister strips in outer carton until required for use.
Protect from light.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER
45/7.3/1119

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION
LeBasi Pharmaceuticals CC
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DATE OF PUBLICATION OF THE PACKAGE INSERT
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Patient Information Leaflet for ZOLMIFOR ODT

SCHEDULING STATUS
S4

PROPRIETARY NAME, STRENGTH AND PHARMACEUTICAL FORM
ZOLMIFOR ODT orodispersible tablet

Read all of this leaflet carefully before you start taking ZOLMIFOR ODT.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- **ZOLMIFOR ODT** has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

1. WHAT ZOLMIFOR ODT CONTAINS
Active ingredient:
Each orodispersible tablet contains 2,5 mg zolmitriptan.

Inactive ingredients:
Aspartame (NutraSweet), basic butylated methacrylate copolymer, low substituted hydroxypropyl cellulose, magnesium aluminometasilicate, magnesium stearate, mannitol, peppermint flavour, silica colloidal anhydrous, sodium laurilsulfate and talc.
Contains artificial sweetener (aspartame).
Sugar free.

2. WHAT ZOLMIFOR ODT IS USED FOR
ZOLMIFOR ODT is used to treat migraine headaches.
ZOLMIFOR ODT will only treat a headache that has already begun. It **will not prevent** headaches or reduce the number of attacks.
ZOLMIFOR ODT should not be used to treat common tension headaches or any headache that seems to be different from your usual migraine headaches. Use **ZOLMIFOR ODT** only if your condition has been confirmed by a doctor as migraine headaches.

3. **BEFORE YOU TAKE ZOLMIFOR ODT**:
Do not take **ZOLMIFOR ODT**:
- If you are allergic (hypersensitive) to zolmitriptan or any of the ingredients of **ZOLMIFOR ODT** (see **WHAT ZOLMIFOR ODT CONTAINS**).
- If you have high blood pressure.
- If you have a heart disorder.
- If you have a heart disorder called angina.
- If you have a moderate to severe liver disorder.
- If you have had a stroke or short-lasting symptoms similar to a stroke (transient ischaemic attack).
- If you are taking medicine called ergotamine or ergotamine-derived products (used for the treatment of migraine).
- If you are using medicine for the prevention and treatment of nausea and vomiting called 5-HT_1 receptor antagonists.
- If you have a condition called Wolff-Parkinson-White syndrome, where you experience an irregular heartbeat, shortness of breath and fainting.

Take special care with ZOLMIFOR ODT:
- If you have other heart disorders. Your doctor will decide if **ZOLMIFOR ODT** is suitable in your condition.
- If you have a liver disorder.
- If you use **ZOLMIFOR ODT** too often, you may experience headaches more often, and it may be necessary to stop using **ZOLMIFOR ODT**.
- If you are taking any medicine for the treatment of depression (see **Taking other medicines with ZOLMIFOR ODT**).
- Safety and efficacy of **ZOLMIFOR ODT** in individuals aged over 65 years have not been confirmed.

Taking ZOLMIFOR ODT with food and drink:
ZOLMIFOR ODT can be taken with or without water (see **HOW TO TAKE ZOLMIFOR ODT**).

Pregnancy and breastfeeding:
If you are pregnant or breastfeeding your baby, please consult your doctor, pharmacist or other healthcare professional for advice before taking **ZOLMIFOR ODT**.

Driving and using machinery:
Take care when driving or using machines that require concentration as **ZOLMIFOR ODT** may cause drowsiness.

Important information about some of the ingredients of ZOLMIFOR ODT:
ZOLMIFOR ODT contains aspartame (which is a source of phenylalanine). If you have an inherited illness called phenylketonuria, consult your doctor before taking **ZOLMIFOR ODT**.

Taking other medicines with ZOLMIFOR ODT:
Always tell your healthcare professional if you are taking any other medicine. (This includes complementary or traditional medicines.)
- **Do not** take the herbal medicine St John's wort (*Hypericum perforatum*) at the same time, because it may result in undesirable effects.
- **Do not** take more than two **ZOLMIFOR ODT** tablets in 24 hours if you are taking a monoamine oxidase inhibitor (used to treat depression).
- **Do not** take more than two **ZOLMIFOR ODT** tablets in 24 hours if you are taking cimetidine (used to treat heartburn or a stomach ulcer) or other medicines such as fluvoxamine (used to treat depression) or certain antibiotics such as ciprofloxacin.
- It is advised to take ergotamine-derived products also used for migraine prevention at least 6 hours after taking **ZOLMIFOR ODT**.

Not all medicines that may interact with ZOLMIFOR ODT are listed above.

4. HOW TO TAKE ZOLMIFOR ODT
Do not share medicines prescribed for you with any other person. Always take **ZOLMIFOR ODT** exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.
The recommended dose of **ZOLMIFOR ODT** to treat a migraine attack is one tablet (2,5 mg).
If a patient does not achieve satisfactory relief with one tablet (2,5 mg doses), subsequent attacks can be treated with two tablets (5 mg doses) of **ZOLMIFOR ODT**.

ZOLMIFOR ODT is effective whenever the tablets are taken during a migraine attack; although it is advisable that the **ZOLMIFOR ODT** orodispersible tablets are taken as early as possible alter the onset of migraine headache.
The blister pack of **ZOLMIFOR ODT** should be peeled open as shown on the foil (the tablets should not be pushed through the foil). The tablet should be placed on the tongue, where it will dissolve and be swallowed with the saliva.
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 you have the impression that the effect of **ZOLMIFOR ODT** is too strong or too weak, tell your doctor or pharmacist.

If you take more ZOLMIFOR ODT than you should:
In the event of an overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison centre.

If you forget to take ZOLMIFOR ODT:
Do not take a double dose of **ZOLMIFOR ODT** to make up for forgotten individual doses.

5. POSSIBLE SIDE EFFECTS
ZOLMIFOR ODT can have side effects.
Not all side effects reported for ZOLMIFOR ODT are included in this leaflet.
Should your general health worsen or if you experience any untoward effects while taking ZOLMIFOR ODT, please consult your doctor, pharmacist or other healthcare professional for advice.
If any of the following happens, stop taking **ZOLMIFOR ODT** and tell your doctor immediately or go to the casualty department at your nearest hospital:
- Swelling of your hands, feet, ankles, face, lips, mouth or throat, which may cause difficulty in swallowing or breathing.
- Rash or itching.
- Fainting.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to **ZOLMIFOR ODT**. You may need urgent medical attention or hospitalisation.

Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:
Frequent:
- Difficulty in breathing.

Less frequent:
- An abnormal heartbeat, increase in heart rate, chest pain.
- Water retention causing swelling of the limbs.
- Increased urination, increased urge to urinate and increase volume of urine.
- Increase in blood pressure.

These are all serious side effects. You may need urgent medical attention.

Tell your doctor as soon as possible if you notice any of the following:
Frequent:
- Abnormalities of the senses including dizziness, sensation of tingling, drowsiness, a warm sensation, headache.
- Dry mouth, nausea, vomiting, difficulty in swallowing, upset stomach or indigestion, abdominal pain.
- Muscle weakness or muscle pain.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

6. STORING AND DISPOSING OF ZOLMIFOR ODT
Store at or below 25 °C.
Keep blister strips in outer carton until required for use.
Protect from light.
STORE ALL MEDICINES OUT OF REACH OF CHILDREN.

7. PRESENTATION OF ZOLMIFOR ODT
ZOLMIFOR ODT is packed into Alu/Alu blister strips and placed into an outer carton, each carton contains 6 tablets.

8. IDENTIFICATION OF ZOLMIFOR ODT
White to off-white, round shaped, flat face bevelled edge tablets, debossed with '2.5' on one side and having a characteristic peppermint flavour.

9. REGISTRATION NUMBER
45/7.3/1119

10. NAME AND ADDRESS OF REGISTRATION HOLDER
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