1. NAME OF THE MEDICINAL PRODUCT

Almovitae 12.5 mg Film-coated tablet.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains almotriptan 12.5 mg as almotriptan D,L-hydrogen malate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White, circular, biconvex film-coated tablet with an “A” engraved on one side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Acute treatment of the headache phase of migraine attacks with or without aura.

4.2. Posology and method of administration

Almovitae should be taken with liquids as early as possible after the onset of migraine-associated headache but it is also effective when taken at a later stage.

Almotriptan should not be used for migraine prophylaxis.

The tablets can be taken with or without food.

Adults (18-65 years of age)

The recommended dose is one tablet containing 12.5 mg of almotriptan. A second dose may be taken if the symptoms reappear within 24 hours. This second dose may be taken provided that there is a minimum interval of two hours between the two doses.

The efficacy of a second dose for the treatment of the same attack when an initial dose is ineffective has not been examined in controlled trials. Therefore if a patient does not respond to the first dose, a second dose should not be taken for the same attack.

The maximum recommended dose is two doses in 24 hours.

Children and adolescents (under 18 years of age)

There are no data concerning the use of almotriptan in children and adolescents, therefore its use in this age group is not recommended.

Elderly (over 65 years of age)

No dosage adjustment is required in the elderly. The safety and effectiveness of almotriptan in patients older than 65 years has not been systematically evaluated.

Renal Impairment

Dosage adjustment is not required in patients with mild or moderate renal impairment. Patients with severe renal impairment should take no more than one 12.5 mg tablet in a 24 hour period.

Hepatic Impairment

There are no data concerning the use of almotriptan in patients with hepatic impairment (see Section 4.3 Contraindications and 4.4 Special warning and precautions for use).

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

As with other 5-$HT_{1B/1D}$ receptor agonists, almotriptan should not be used in patients with a history, symptoms or signs of ischaemic heart disease (myocardial infarction, angina pectoris, documented silent ischaemia, Prinzmetal's angina) or severe hypertension and uncontrolled mild or moderate hypertension.

Patients with a previous cerebrovascular accident (CVA) or transient ischaemic attack (TIA). Peripheral vascular disease.

Concomitant administration with ergotamine, ergotamine derivatives (including methysergide) and other 5-$HT_{1B/1D}$ agonists is contraindicated.

Patients with severe hepatic impairment (see Section 4.2. Posology and method of administration).

4.4. Special warnings and precautions for use

Almotriptan should only be used where there is a clear diagnosis of migraine. It should not be used to treat basilar, hemiplegic or ophthalmoplegic migraine.

As with other acute migraine therapies, before treating headaches in patients not previously diagnosed as migraine sufferers and in migraine sufferers who present atypical symptoms, care should be taken to exclude other potentially serious neurological conditions. Cerebrovascular accidents have been reported in patients treated with $5HT_{1B/1D}$ agonists. It should be noted that migraineurs may be at increased risk of certain cerebrovascular events (e.g. cerebrovascular accident, transient ischemic attack).

In very rare cases, as with other 5-$HT_{1B/1D}$ receptor agonists, coronary vasospasm and myocardial infarction have been reported. Therefore almotriptan should not be administered to patients who could have an undiagnosed coronary condition without prior evaluation of potential underlying cardiovascular disease. Such patients include postmenopausal women, males over 40 and patients with other risk factors for coronary disease such as uncontrolled hypertension, hypercholesterolaemia, obesity, diabetes,

smoking or a clear family history of cardiovascular disease. These evaluations however, may not identify every patient who has cardiac disease and in very rare case, serious cardiac events have occurred in patients without underlying cardiovascular disease when 5-HT_1 agonists have been administered.

Following administration, almotriptan can be associated with transient symptoms including chest pain and tightness which may be intense and involve the throat (see Section 4.8 Undesirable effects). Where such symptoms are thought to indicate ischaemic heart disease, no further dose should be taken and appropriate evaluation should be carried out.

Caution should be exercised when prescribing almotriptan to patients with known hypersensitivity to sulphonamides.

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 noradrenaline reuptake inhibitors (SNRIs). These reactions can be severe. If concomitant treatment with almotriptan and a 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 serotoninergic medication (See Section 4.5).

It is advised to wait at least 6 hours following use of almotriptan before administering ergotamine. At least 24 hours should elapse after the administration of an ergotaminecontaining preparation before almotriptan is given. Although additive vasospastic effects were not observed in a clinical trial in which 12 healthy subjects received oral almotriptan and ergotamine, such additive effects are theoretically possible (see Section 4.3 Contraindications).

Patients with severe renal impairment should not take more than one 12.5 mg tablet in a 24 hour period.

Caution is recommended in patients with mild to moderate hepatic disease and treatment is contraindicated in patients with severe hepatic disease (see section 5.2 Pharmacokinetic properties).

Undesirable effects may be more common during concomitant use of triptans and herbal preparations containing St John's Wort (*Hypericum perforatum*).

As with other 5-$HT_{1B/1D}$ receptor agonists, almotriptan may cause mild, transient increases in blood pressure, which may be more pronounced in the elderly.

Medication overuse headache (MOH)
Prolonged use of any painkiller for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained and treatment should be discontinued. The diagnosis of MOH should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

The maximum recommended dose of almotriptan should not be exceeded.

This medicine contains less than 1mmol sodium (23 mg) per tablet, that is to say essentially 'sodium free'.

4.5. Interaction with other medicinal products and other forms of interaction

Interaction studies were performed with monoamine oxidase A inhibitors, beta-blockers, selective serotonin re-uptake inhibitors, calcium channel blockers or inhibitors of Cytochrome P450 isoenzymes 3A4 and 2D6. There are no *in vivo* interaction studies assessing the effect of almotriptan on other drugs.

As with other 5-HT_1 agonists, the potential risk of a serotoninergic syndrome due to a pharmacodynamic interaction in case of concomitant treatment with MAOIs cannot be ruled out.

There have been reports describing patients with symptoms compatible with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the use of selective serotonin reuptake inhibitors (SSRIs) or serotonin noradrenaline reuptake inhibitors (SNRIs) and triptans (see Section 4.4).

Multiple dosing with the calcium channel blocker verapamil, a substrate of CYP3A4, resulted in a 20% increase in C_{max} and AUC of almotriptan. The increase is not considered clinically relevant. No clinically significant interactions were observed.

Multiple dosing with propranolol did not alter the pharmacokinetics of almotriptan. No clinically significant interactions were observed.

In vitro studies performed to evaluate the ability of almotriptan to inhibit the major CYP enzymes in human liver microsomes and human monoamine oxidase (MAO) showed that almotriptan would not be expected to alter the metabolism of drugs metabolised by CYP or MAO-A and MAO-B enzymes.

4.6. Fertility, pregnancy and lactation

Pregnancy

For almotriptan, very limited data on pregnant patients are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).
Caution should be exercised when prescribing almotriptan to pregnant women.

Breast-feeding

There are no data regarding excretion of almotriptan in human milk. Studies in rats have shown that almotriptan and/or its metabolites are excreted in milk.

Caution should therefore be exercised when prescribing during lactation. Infant exposure may be minimised by avoiding breast feeding for 24 hours after treatment.

4.7. Effects on ability to drive and use machines

There are no studies on the effect of almotriptan on the ability to drive or operate machinery. However, since somnolence may occur during a migraine attack and has been reported as a side effect of treatment with almotriptan, caution is recommended in patients performing skilled tasks.

4.8. Undesirable effects

Almogran/Amignul was evaluated in over 2700 patients for up to one year in clinical trials. The most common adverse reactions at the therapeutic dose were dizziness, somnolence, nausea, vomiting and fatigue. None of the adverse reactions had an incidence superior to 1.5%.

The following adverse reactions have been evaluated in clinical studies and/or reported in post-marketing experience. They have been listed by System Organ Class (SOC) and in descending order of frequency. Frequencies are defined as: very common (>1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

System Organ Class	**Common**	**Uncommon**	**Very rare**	**Not known**
Immune system disorders				Hypersensitivity reactions (including angioedema) Anaphylactic reactions
Nervous system disorders	Dizziness Somnolence	Paraesthesia Headache		Seizures
Eye disorders				Visual impairment* Vision blurred*
Ear and labyrinth disorders		Tinnitus		
Cardiac disorders		Palpitations	Coronary vasospasm Myocardial infarction Tachycardia	
Respiratory, thoracic and mediastinal disorders		Throat tightness		
Gastrointestinal Disorders	Nausea Vomiting	Diarrhoea Dyspepsia Dry mouth		Intestinal ischemia
Musculoskeletal, connective tissue and bone disorders		Myalgia Bone pain		
General Disorders	Fatigue	Chest pain Asthenia		

** However visual disorders may also occur during a migraine attack itself.*

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the HPRA Pharmacovigilance, Website: www.hpra.ie

4.9. Overdose

The most frequently reported adverse event in patients receiving 150 mg (the highest dose administered to patients) was somnolence.

Overdose should be treated symptomatically and vital functions should be maintained. Since the elimination half-life is around 3.5 hours monitoring should continue for at least 12 hours or while symptoms or signs persist.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antimigraine. Selective 5-HT_1 receptor agonist.

ATC code: N02CC05.

Mechanism of action

Almotriptan is a selective 5-HT_{1B} and 5-HT_{1D} receptor agonist. These receptors mediate vasoconstriction of certain cranial vessels, as demonstrated in studies using isolated human tissue preparations. Almotriptan also interacts with the trigeminovascular system, inhibiting extravasation of plasma proteins from dural vessels following trigeminal ganglionic stimulation, which is a feature of neuronic inflammation that seems to be involved in the physiopathology of migraine. Almotriptan has no significant activity on other 5-HT receptor subtypes and no significant affinity for adrenergic, adenosine, angiotensin, dopamine, endothelin or tachykinin binding sites.

Pharmacodynamic effects

The efficacy of almotriptan in the acute treatment of migraine attacks was established in four multicentre, placebo-controlled clinical trials including more than 700 patients who were administered 12.5 mg. The decrease in pain began 30 minutes after administration, and the percentage of response (reduction of headache from moderate-severe to mild or absent) after 2 hours was 57-70% with almotriptan and 32-42% after placebo. In addition, almotriptan relieved nausea, photophobia and phonophobia associated with migraine attacks.

5.2. Pharmacokinetic properties

Almotriptan is well absorbed, with an oral bioavailability of about 70%. Maximum plasma concentrations (C_{max}) occur approximately between 1.5 and 3.0 hours after administration. The rate and extent of absorption is unaffected by concomitant ingestion of food. In healthy subjects administered single oral doses ranging from 5 mg to 200 mg, C_{max} and AUC were proportional to dose, indicating linear pharmacokinetic behaviour. The elimination half-life ($t_{1/2}$) is about 3.5 h in healthy subjects. There is no evidence of any gender-related effect on the pharmacokinetics of almotriptan.

More than 75% of the dose administered is eliminated in urine, and the remainder in faeces. Approximately, the 50% of the urinary and faecal excretion is unchanged almotriptan. The major biotransformation route is via monoamine oxidase (MAO-A) mediated oxidative deamination to the indole acetic metabolite. Cytochrome P450 (3A4 and 2D6 isozymes) and flavin mono-oxygenase are other enzymes involved in the

metabolism of almotriptan. None of the metabolites is significantly active pharmacologically.

After an intravenous dose of almotriptan administered to healthy volunteers the average values for the distribution volume, total clearance and elimination half-life were 195 L, 40 L/h and 3.4 h respectively. Renal clearance (CL_R) accounted for about two-thirds of total clearance and renal tubular secretion is probably also involved. The CL_R correlates well with renal function in patients with mild (creatinine clearance: 60-90 ml/min), moderate (creatinine clearance: 30-59 ml/min) and severe (creatinine clearance: < 30 ml/min) renal impairment. The increase of the mean $t_{1/2}$ (up to 7 hours) is statistically and clinically significant in the case of patients with severe renal impairment only. Compared with healthy subjects, the increase in the maximum plasma concentration (C_{max}) of almotriptan was 9%, 84% and 72% respectively for patients with slight, moderate and severe renal impairment, whereas the increase in exposure (AUC) was 23%, 80% and 195% respectively. According to these results, the reduction of the total clearance of almotriptan was -20%, -40% and -65% respectively for patients with slight, moderate and severe renal impairment. As expected, total (CL) and renal (CL_R) clearances were reduced but without clinical relevance in healthy elderly volunteers compared with a young control group.

Based on the mechanisms of almotriptan clearance in man, approximately 45% of almotriptan elimination appears to be due to hepatic metabolism. Therefore, even if these clearance mechanisms were totally blocked or impaired, plasma almotriptan levels would be increased a maximum of two-fold over the control state, assuming that renal function (and almotriptan renal clearance) are not altered by hepatic impairment. In patients with severe renal impairment, C_{max} is increased twofold, and AUC is increased approximately threefold relative to healthy volunteers. Maximal changes in pharmacokinetic parameters in patients with significant hepatic impairment would not exceed these ranges. For this reason, no study of the pharmacokinetics of almotriptan in patients with hepatic impairment was performed.

5.3. Preclinical safety data

In safety pharmacology, repeated dose toxicity and reproduction toxicity studies, adverse effects were observed only at exposures well above the maximum human exposure.

Almotriptan did not show any mutagenic activity in a standard battery of *in vitro* and *in vivo* genotoxicity studies, and no carcinogenic potential was revealed in studies conducted in mice and rats.

As occurs with other 5-$HT_{1B/1D}$ receptor agonists, almotriptan binds to melanin. However, no ocular adverse effects associated with the drug have been observed in dogs after treatment for up to one year.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Tablet core:
Mannitol (E-421)
Microcrystalline cellulose
Povidone
Sodium starch glycolate

Sodium stearyl fumarate

Coating material:
Hypromellose
Titanium dioxide (E-171)
PEG 400

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

48 months.

6.4. Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5. Nature and contents of container

Boxes containing aluminium foil blisters with 10 tablets.

6.6. Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Galenicum Health, S.L

8. DATE OF REVISION OF THE TEXT

January 2021