SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Olcadil 2 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg of cloxazolam.

Excipients with known effect:
Lactose - 99.94 mg (as lactose anhydrous).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
Pink, circular, flat tablet, with edge, inscription "Sandoz" on one side and a score line on the other.
The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Emotional disorders, such as anxiety, tension, agitation.

- Sleep disorders, such as difficulty falling asleep, insomnia and early morning awakening.

Benzodiazepines are only indicated when the disease is serious, incapacitating or when the patient is subject to extreme anguish.

Other indications:
- Pre-medication before surgical intervention.

4.2 Posology and method of administration

Emotional disorders, such as anxiety, tension, agitation

Treatment should be as short as possible. The patient should be regularly assessed and the need to continue treatment should be assessed, especially if the patient is symptom-

free. Overall treatment duration should not exceed 8-12 weeks, including progressive dose reduction.

In certain cases it may be necessary to prolong treatment beyond the period indicated: if this happens, it should not take place before a reassessment of the patient by a specialist.

Sleep disorders, such as difficulty falling asleep, insomnia and early morning awakening

Treatment should be as short as possible. In general, treatment duration varies between a few days and two weeks, with a maximum of four weeks including gradual reduction of the medicinal product.

In certain situations, treatment prolongation may be required, in this case, it should not be done without a reassessment of the patient's condition.

Treatment should be started with the minimum recommended dose. The maximum recommended dose should not be exceeded.

- Symptoms of mild to moderate severity: 3 to 6 mg daily, divided in two administrations (if necessary three).

- Symptoms of moderate to severe severity: 6 to 8 mg daily, divided in two administrations (if necessary three).

The optimal therapeutic dose should be individually determined by a gradual adjustment.

Maximum recommended dose: 12 mg/day.

In case of improvement (after 2 to 6 weeks), the dose may be gradually reduced until complete treatment discontinuation.

Pre-medication before surgical intervention

If oral administration is possible, 0.1 mg/kg of body weight is recommended one to two hours before a surgical intervention. In cases of marked anxiety, the same dose may also be administered on the day before the intervention.

In elderly patients, a dosage decrease is recommended. In cases of hepatic or renal disease, patients should be carefully monitored and, if necessary, the dosage should be reduced.

When long-term benzodiazepines, such as Olcadil, are used, the patient should be regularly monitored in the beginning of the treatment, in order to decrease the dose or the frequency of administration, in case it is necessary to prevent an overdose due to accumulation.

4.3 Contraindications

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

- Severe Central Nervous System depression.
- Myasthenia gravis.
- History of hypersensitivity to benzodiazepine derivatives.
- Severe respiratory failure.
- Sleep apnoea syndrome.
- Severe hepatic failure.

4.4 Special warnings and precautions for use

Tolerance
Some decrease in efficacy of the hypnotic effect of benzodiazepines may occur after repeated use for a few weeks.

Dependence and treatment interruption
The use of benzodiazepines may lead to the development of physical and psychic dependence on these drugs. The risk of dependence increases with high doses and prolonged treatment duration and is higher in patients with a history of alcoholism or drug dependence.

If dependence develops, abrupt treatment interruption may be accompanied by withdrawal syndrome. This situation may include headache, myalgia, extreme anxiety, tension, dysphoria, agitation, confusion, irritability, sweating, nausea, vomiting and griping abdomen. In severe conditions, the following symptoms may occur: feeling unreal, depersonalisation, hyperacusia, torpor and paraesthesias of the extremities, hypersensitivity to the light, noise and physical contact, tremor, hallucinations or convulsions.

Rebound insomnia and/or rebound anxiety may occur after treatment interruption with benzodiazepines. This fact may be accompanied by other symptoms such as mood swings, anxiety or sleep disorders and agitation.

Since the risk of withdrawal/rebound syndrome is higher following abrupt treatment discontinuation, gradual dose decrease is recommended.

Treatment duration
Treatment duration should be as short as possible (see section 4.2) depending on the therapeutic indication, but it should not exceed 4 weeks for insomnia and 4 to 6 weeks for anxiety, including a period of gradual dose decrease. Therapy prolongation beyond this period should not occur without previous reassessment of the situation.

It may be useful to tell the patient that the treatment will have a short duration and explain precisely how the dose will be gradually decreased. It is also important that the patient is aware of the possibility of rebound phenomenon occurring during progressive dose reduction, thereby minimising the anxiety associated with this phenomenon.

Risk of foetal problems
Benzodiazepines may cause foetal problems when administered in pregnant women (see section 4.6). Based on the experience with this class of drugs, Olcadil may lead to an increased risk of congenital abnormalities when administered to pregnant women during

the first trimester of pregnancy. Therefore, the use of Olcadil during the first trimester of pregnancy should always be avoided.

The possibility that a woman of childbearing potential may be pregnant early in treatment should always be taken into account. Patients who become pregnant during treatment with Olcadil or that intend to become pregnant should be informed of the potential risk for the foetus and advised to discontinue treatment.

Amnesia
Anterograde amnesia has occurred with therapeutic doses of benzodiazepines. This situation occurs more commonly several hours after drug intake. To reduce this risk, patients should ensure they are able to sleep uninterruptedly for 6 to 8 hours (See also section 4.8).

Psychiatric and paradoxical reactions
Reactions such as jitteriness, agitation, irritability, aggression, illusion, rage attacks, nightmares, hallucinations, psychosis, inappropriate behaviour and other adverse behavioural effects are associated with treatment with benzodiazepines (See also section 4.8). If any of these situations occurs, treatment should be discontinued.

These situations occur more commonly or with more severity in elderly.

Special populations

Paediatric population
The use of Olcadil is not recommended in children.

Geriatric population
Elderly patients may be more susceptible to the benzodiazepines effect, including Olcadil. In epidemiological studies, a significant association between benzodiazepines administration and falls and hip fractures was demonstrated in the elderly. Therefore, these patients should be frequently monitored and their dosage should be adjusted according to treatment response (see section 4.2).

Other populations
Due to risk of respiratory depression, benzodiazepines should be used with extreme precaution in patients with chronic obstructive pulmonary disease or myocardial infarction.

In the presence of renal or hepatic impairment, chronic brain syndrome, or angle closure glaucoma, patients should be closely monitored and, if necessary, the dose of Olcadil should be reduced. There is a risk of cloxazolam accumulation in patients with hepatic and/or renal impairment and the condition may get worse in patients with chronic brain syndrome and angle closure glaucoma, due to the potentiation of GABA, cognitive impairment and anticholinergic properties (see sections 4.2 and 5.2).

Pre-existent depression may return or get worse during the administration of benzodiazepines including Olcadil.

Benzodiazepines should not be used in monotherapy to treat depression or depression-associated anxiety, as it may lead to suicide.

Benzodiazepines should be used with extreme caution in patients with clinical history of alcoholism or drug dependence.

Risk from concomitant use of opioids
Concomitant use of Olcadil 2mg Tablets and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs such as Olcadil 2mg Tablets with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Olcadil 2mg Tablets concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).
The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers (where applicable) to be aware of these symptoms (see section 4.5).

The tablets of Olcadil contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Olcadil may enhance the central inhibitory effects of neuroleptics (antipsychotics), antidepressants, anxiolytics, sedatives, hypnotics, narcotics, analgesics, antiepileptic drugs, anaesthetics and sedative antihistamines. This fact may be used with therapeutic purpose, especially through the association of Olcadil with antidepressants. Precaution should be taken when Olcadil is administered in association with Central Nervous System depressants. In the case of narcotic analgesics, enhanced euphoria may occur which may lead to increased psychic dependence.

Concomitant administration of Olcadil with antihypertensive medicinal products (for example, clonidine, pindolol, dihydralazine, diuretics and metoprolol) did not show significant changes in blood pressure, in undesirable effects and in ECG parameters.

Concomitant administration of Olcadil with anticoagulant medicinal products did not show significant changes in prothrombin time.

Concomitant alcohol intake is not recommended (see section 4.4). The sedative effect may be enhanced when the medicinal product is concomitantly taken with alcohol. This affects the ability to drive or use machines.

Substances that inhibit certain hepatic enzymes (particularly cytochrome P450) may enhance the activity of benzodiazepines. This effect also applies to benzodiazepines metabolised only by conjugation, albeit to a smaller extent.

Opioids
The concomitant use of sedative medicines such as benzodiazepines or related drugs such as Olcadil 2mg Tablets with opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing age
If the drug is prescribed to a woman of childbearing age, she should be advised to contact her doctor regarding treatment discontinuation if she intends to become pregnant or suspects that she is pregnant.

Pregnancy
Benzodiazepines may cause foetal problems when administered to pregnant women. Animal studies did not reveal teratogenic potential (see section 5.3), although data on Olcadil administration to pregnant women are limited.

Based on the experience with other benzodiazepines, Olcadil may lead to an increased risk of congenital abnormalities when administered to pregnant women during the first trimester of pregnancy.

New-borns of mothers who took benzodiazepines chronically during the latter stage of pregnancy may develop physical dependence and may be at risk of developing withdrawal symptoms in the postnatal period. The following cases were reported in new-borns of mothers who took benzodiazepines: neonatal flaccidity, hypothermia, low birth weight and respiratory problems.

Breastfeeding
It is likely that Olcadil is excreted in human milk (see section 5.2). Due to the potential of severe adverse reactions in infants (or tumorigenicity in animals), it should be decided whether to discontinue breastfeeding or the medicinal product, taking into account the importance of the medicinal product to the mother.

Chronic administration of benzodiazepines to breastfeeding mothers was reported as being the cause of lethargy, weight loss and decreased sucking reflex in infants.

Since benzodiazepines are excreted in breast milk, they should not be administered to breastfeeding mothers.

Fertility
The administration of cloxazolam in rats did not have an effect on male and female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Especially in high doses, Olcadil, as all central-acting medicinal products, may affect the patients' reactions when driving vehicles and using machines.

Sedation, amnesia, concentration difficulty, diplopia and impaired muscle function may adversely affect the ability to drive or use machines.

The sedative effect may increase when Olcadil is concomitantly administered with alcohol. This situation affects the ability to drive and use machines (see section 4.5).

4.8 Undesirable effects

Summary of the safety profile

The following undesirable effects are the most commonly observed: somnolence, fatigue, headaches, dizziness, muscle tone decreased, ataxia and disorders of accommodation. These effects occur mainly in early treatment and generally disappear with continued treatment. Other undesirable effects were occasionally reported such as gastrointestinal disorders, libido disorders or skin reactions

Summary table of undesirable effects from clinical trials

Undesirable effects from clinical trials (Table 1) are listed by system organ class according to the MedDRA database. The MedDRA version used is 16.0. In each system organ class, undesirable effects are rated according to frequency, with the most common reaction first. Within each frequency group, undesirable effects are presented by decreasing order of seriousness. Additionally, frequency categories for each undesirable effect are based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 1 - Undesirable effects most commonly reported than with placebo in clinical trials

Metabolism and nutrition disorders Very common: decreased appetite
Nervous system disorders Very common: somnolence, headache, dizziness
Eye disorders Common: accommodation disorders
Vascular disorders Common: orthostatic hypotension
Gastrointestinal disorders Very common: constipation, dry mouth
Skin and subcutaneous tissue disorders Common: hyperhidrosis
Musculoskeletal and connective tissue disorders Common: hypotonia
General disorders and administration site conditions Very common: fatigue

List of undesirable effects from post-marketing spontaneous reports.

The following undesirable effects are from post-marketing experience with Olcadil through spontaneous reports and literature cases. Since these undesirable effects are reported voluntarily from a not known population size, it is not possible to estimate their frequency and they are therefore categorised as not known. Undesirable effects are listed by system organ class according to the MedDRA database. Within each system organ class, undesirable effects are presented in order of decreasing seriousness.

Psychiatric disorders: nervousness, anxiety, agitation, depression, decreased libido, confusional state, hallucinations, illusions, abnormal behaviour, drug dependence, sleep disorders.

Nervous system disorders: tremor, sedation, amnesia, decreased mental function and memory, ataxia.

Eye disorders: cloudy vision and visual impairment

Gastrointestinal disorders: abdominal pain, vomiting

Skin and subcutaneous tissue disorders: skin rash, angioedema, urticaria

Musculoskeletal and connective tissue disorders: musculoskeletal pain

Reproductive system and breast disorders: erectile dysfunction

General disorders and administration site conditions: discomfort, irritability

Investigations: weight increase.

Reporting suspected adverse reactions:
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:
INFARMED, I.P.
Direção de Gestão do Risco de Medicamentos
Parque da Saúde de Lisboa, Av. Brasil 53
1749-004 Lisboa
Tel: +351 21 798 7373
Linha do medicamento: 800222444
Website: http://www.infarmed.pt/web/infarmed/submissaoram
E-mail: farmacovigilancia@infarmed.pt

4.9 Overdose

Benzodiazepine overdose is usually manifested by several degrees of Central Nervous System depression, varying from somnolence to coma. In mild situations, symptoms include somnolence, mental confusion and lethargy. In more severe cases, and especially if alcohol or other medicinal products are ingested, symptoms may include ataxia, hypotonia, hypotension, cardiovascular depression, respiratory depression, hypnotic state, coma and death.

As in the management of situations of intentional overdose, it must be taken into account that multiple medicinal products may have been taken.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nervous System. Psycholeptics. Anxiolytics. Benzodiazepine derivatives, ATC code: N05B A22

Mechanism of action

From a large number of electrophysiological investigations, it was demonstrated that benzodiazepines promote the action of the neurotransmitter gamma-aminobutyric acid (GABA) in their receptors. Since this enhancing effect of GABA was discovered in many different biological systems, it is currently believed that benzodiazepines produce their identifiable effects through the modulation of the GABA system in the brain.

Olcadil has tranquilliser and anticonvulsant properties. Neurophysiological studies have demonstrated that these two effects are due to an inhibition of the limbic system and hypothalamus; the sedative effects (inhibition of wake system) are less marked.

Olcadil has a weaker muscle relaxant effect than the classic tranquillisers. In therapeutic doses, Olcadil mainly eliminates anxiety, tension and several types of insomnia, usually without causing somnolence or ataxia.

Clinical trials

The results of three different double-blind, multicentre, placebo-controlled, studies with parallel groups of flexible dose for Olcadil 2-12 mg/day in patients with moderate to severe chronic state of phobic or diffuse anxiety (N=183) were pooled. For patients treated with Olcadil, an improvement of ≥60% was observed, from the beginning until the end of the study (day 42), in 21 of the 33 items assessed in the Sandoz list of symptoms (SCL). These include 8 symptoms related to anxiety or fear, the totality of the 3 symptoms associated with sleep disorders and 4 symptoms related to depressive symptoms and social maladjustment. With exception of psychomotor retardation and decreased libido, a marked improvement for all symptoms from the beginning of treatment with Olcadil compared to placebo was observed; this improvement was statistically significant in 26 of the 33 symptoms assessed on day 42. A significant improvement was seen in the group treated with Olcadil compared to the placebo-treated group shortly on day 7 for 4 symptoms (feelings of discouragement, pain sensations, inner agitation and early morning awakening), with most of the symptoms also showing improvement on that level on day 14 and day 21.

The subgroup analysis of syndromes showed a statistically significant improvement from the beginning of the study until day 42 for patients treated with Olcadil compared to placebo in affectivity, sleep, thinking process, content of thoughts and social behaviour. Except for thinking process and social behaviour, this improvement was also seen for other assessments shortly after the beginning of the study (i.e. day 7, 14 and 21). A statistically significant improvement was also observed in favour of Olcadil in the total SCL score, in all time points after the beginning of the trial.

The analysis of the total score of the Zung Self-Evaluation Scale (of the patient) showed an improvement from the beginning of the study until day 42 of 58% and 35% for Olcadil and placebo, respectively. The difference between Olcadil and placebo was statistically significant on day 14, 21 and 42.

The total subjective evaluation, as determined by Gravity Mental Disease Scale of Early Clinical Drug Evaluation Program (ECDEU) demonstrated a statistically significant improvement from the beginning until day 42 for the group treated with Olcadil compared to the placebo group (51% and 23%, respectively).

5.2 Pharmacokinetic properties

Absorption

Cloxazolam is rapidly absorbed, following oral administration of 14C-Olcadil in humans and about 50% of the radiolabeled drug was excreted in urine. Radioactivity studies performed in animals confirmed that more than 75% of the drug is absorbed following oral administration. Peak plasma concentrations of the active metabolite (chloro-N-desmethyldiazepam) are reached within 2 to 3h following a dose of Olcadil, indicating that the drug suffers a rapid metabolism.

Biotransformation

Two routes were identified in the rapid metabolism of cloxazolam. The first route leads to hydroxylation of the drug and consequently results in formation of chloro-N-desmethyldiazepam (CND). This hydroxy derivative is partially glucuronidated and eliminated in bile. The second route leads to the formation of amino-benzophenone derivative that suffers conjugation after cleavage of the core of diazepam and consequent hydroxylation.

Cloxazolam is rapidly metabolised into its biggest metabolite, chloro-desmethyldiazepam (CND) resulting in a measurable low level of unchanged drug in plasma. The active metabolite (CND) has about 1000 times more affinity for the benzodiazepine receptors than cloxazolam itself.

Distribution

Maximum plasma concentration of the active metabolite (CND) reaches 7.79 ± 1.6 ng/mL following a single oral administration of 2 mg of cloxazolam. Following administration of 1 mg of cloxazolam, 3 times daily, steady state concentrations are reached in 8 to 10 days. Plasma concentrations of the active metabolite reach a level between 24 to 26 ng/mL.

The binding of cloxazolam and the active metabolite (CND) to plasma proteins is 96% and 94%, respectively.

Passage into milk

Data available for animals demonstrate that cloxazolam is excreted into female rats milk. The extrapolation of the results from female rats to humans indicates that the infant can ingest a maximum of 0.1% of the maternal dose of cloxazolam. However, a risk for the infant cannot be excluded (see section 4.6).

Elimination
The drug is mainly excreted via the bile and only a small percentage of the dose is excreted via the kidneys (about 18%). The active metabolite, CND, is eliminated in a bi-exponential model with a slow elimination half-life of about 66 hours. Chronic administration of cloxazolam indicates that there is no accumulation of the drug and that there is no impact on its own metabolism.

Special populations

Paediatric population
The pharmacokinetics of Olcadil was not studied in the paediatric population.

Patients with hepatic impairment
The main metabolite of Olcadil (CND) was orally administered to 6 patients with hepatic impairment and intravenously to 2 patients with hepatic impairment. Although there is a great variability in the data, most patients with hepatic disease showed a slower total clearance of CND and a prolonged elimination half-life. Although these results have been only obtained following the administration of the main active metabolite of Olcadil, precautions should be taken when Olcadil is administered in this population.

Patients with renal impairment
The pharmacokinetics of Olcadil has not been studied in this population. Therefore, the elimination half-lime may increase, and precautions should be taken when Olcadil is administered in this population.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional single and repeated dose toxicity, mutagenic and carcinogenic potential.

The administration of cloxazolam in rats has no adverse effects on male or female fertility and there were no indications of teratogenic potential in mice, rats and rabbits. The decrease of perinatal survival in rats was attributed to cloxazolam tranquilizer effect on the mother during labour and postnatal period, since the effect on the survival of the offspring has not been demonstrated when treatment was interrupted before delivery.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Magnesium stearate
Talc
Hydroxypropylcellulose
Maize starch
Lactose anhydrous
Red iron oxide (E172).

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
1 year

6.4 Special precautions for storage
Do not store above 25ºC.

6.5 Nature and contents of container
Olcadil is presented in packages containing 20, 40 and 60 circular, pink, flat tablets, with edge, inscription "Sandoz" on one side and a score line on the other, packed in PVC/PVDC/Aluminium blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
No special requirements for disposal. Any unused medicinal products or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER
Phoenix Labs
Suite 12, Bunkilla Plaza,
Bracetown Business Park,
Clonee, County Meath,
Ireland

8. MARKETING AUTHORISATION NUMBER(S)
Registration no: 9570044 - 20 tablets, 2 mg, PVC/PVDC/Alu blisters
Registration no: 4619896 - 40 tablets, 2 mg, PVC/PVDC/Alu blisters
Registration no: 9570051 - 60 tablets, 2 mg, PVC/PVDC/Alu blisters

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of the first authorisation: 13th July 1983
Date of the last renewal: 9th February 2001

10. DATE OF REVISION OF THE TEXT

13th December 2018