

## Summary of Product Characteristics

### 1. Name of the medicinal product

ANAXAL 0,25 mg; 0,5 mg and 1 mg tablets

### 2. Qualitative and quantitative composition

Each tablet contains 500 micrograms alprazolam.

For the full list of excipients, see section 6.1

### 3. Pharmaceutical form

Tablet

### 4. Clinical particulars

#### 4.1 Therapeutic indications

ANAXAL is indicated for the short-term treatment of moderate or severe anxiety states and anxiety associated with depression. It is only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.

ANAXAL should not be used to treat short-term mild anxiety, such as anxiety or tension associated with the stress of everyday life. As the efficacy of ANAXAL in depression and in phobic or obsessional states has yet to be established, specific treatment may have to be considered.

#### 4.2 Posology and method of administration

##### Posology

###### *Anxiety*

250 micrograms (0.25 mg) to 500 micrograms (0.5 mg) three times daily, increasing if required to a total of 3 mg daily.

###### *The elderly or in the presence of debilitating disease*

250 micrograms (0.25 mg) two to three times daily to be gradually increased if needed and tolerated.

If side-effects occur, the dose should be lowered. It is advisable to review treatment regularly and to discontinue use as soon as possible. Should longer term treatment be necessary, then intermittent treatment may be considered to minimize the risk of dependence.

###### *Paediatric population*

The safety and efficacy of alprazolam in children and adolescents below the age of 18 years have not been established. No data are available.

##### Method of administration

For oral use.

Treatment should be as short as possible. It is recommended that the patient be reassessed at the end of no longer than 4 weeks of treatment and the need for continued treatment established, especially in case the patient is symptom free. The overall duration of treatment should not be more than 8-12 weeks, including a tapering off process.

In certain cases extension beyond the maximum treatment period may be necessary; if so, it should not take place without re-evaluation of the patient's status with special expertise. As with all benzodiazepines, physicians should be aware that long-term use might lead to dependence in certain patients.

The optimum dosage of ANAXAL should be based upon the severity of the symptoms and individual patient response. The lowest dose which can control symptoms should be used. Dosage should be reassessed at intervals of no more than 4 weeks. The usual dosage is stated below; in the few patients who require higher doses, the dosage should be increased cautiously to avoid adverse effects. When higher dosage is required, the evening dose should be increased before the daytime doses. In general, patients who have not previously received psychotropic medications will require lower doses than those so treated, or those with a history of chronic alcoholism.

Treatment should always be tapered off gradually. During discontinuation of alprazolam treatment, the dosage should be reduced slowly in keeping with good medical practice. It is suggested that the daily dosage of alprazolam be decreased by no more than 0.5 mg every three days. Some patients may require an even slower dosage reduction (see section 4.4).

#### *Elderly patients*

There is a reduced clearance of the drug and, as with other benzodiazepines, an increased sensitivity to the drug in elderly patients. See section 5.2.

### **4.3 Contraindications**

Hypersensitivity to benzodiazepines, alprazolam, or to any of the excipients listed in section 6.1. Benzodiazepines are also contraindicated in patients with myasthenia gravis, severe respiratory insufficiency, sleep apnoea syndrome and severe hepatic insufficiency.

### **4.4 Special warnings and precautions for use**

#### *Renal and hepatic impairment*

Caution is recommended when treating patients with impaired renal function or mild to moderate hepatic insufficiency.

#### *Depression/anxiety*

In patients presenting with major depression or anxiety associated with depression benzodiazepines and benzodiazepine-like agents should not be prescribed alone to treat depression as they may precipitate or increase the risk of suicide. Therefore alprazolam should be used with caution and the prescription size should be limited in patients with signs and symptoms of a depressive disorder or suicidal tendencies.

#### *Paediatric population*

Safety and efficacy of alprazolam have not been established in children and adolescents below the age of 18 years; therefore use of alprazolam is not recommended.

#### *Elderly patients*

Benzodiazepines and related products should be used with caution in elderly, due to the risk of sedation and / or musculoskeletal weakness that can promote falls, often with serious consequences in this population.

It is recommended that general principle of using the lowest effective dose to be followed in elderly and /or debilitated patients to preclude development of ataxia or over-sedation (see section 4.2). A lower dose is also recommended for patients with chronic respiratory insufficiency due to risk of respiratory depression.

Benzodiazepines should be used with extreme caution in patients with a history of alcohol or drug abuse (see section 4.5).

#### *Risk from concomitant use of opioids*

Concomitant use of ANAXAL 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 ANAXAL with opioids should be reserved for patients for whom alternative treatment options are not possible.

If a decision is made to prescribe ANAXAL 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 environment to be aware of these symptoms (see section 4.5).

#### *Dependence*

Use of benzodiazepines may lead to the development of physical and psychic dependence upon these products. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a history of alcohol and drug abuse. Pharmacodependency may occur at therapeutic doses and/or in patients with no individualised risk factor. There is an increased risk of pharmacodependency with the combined use of several benzodiazepines regardless of the anxiolytic or hypnotic indication. Cases of abuse have also been reported.

Withdrawal symptoms: Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches, muscle pain, extreme anxiety, tension, restlessness, confusion, irritability and insomnia. In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures (see section 4.2).

During discontinuation of alprazolam treatment, the dosage should be reduced slowly in keeping with good medical practice. It is suggested that the daily dosage of alprazolam be decreased by no more than 0.5 mg every three days. Some patients may require even slower dosage reduction. Rebound insomnia and anxiety: a transient syndrome whereby the symptoms that led to treatment with a benzodiazepine recur in an enhanced form may occur on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety or sleep disturbances and restlessness. Since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage be decreased gradually by no more than 0.5 mg every three days. Some patients may require an even slower dose reduction (see section 4.2).

#### *Duration of treatment*

The duration of treatment should be as short as possible (see section 4.2) depending on the indication, but should not exceed eight to twelve weeks including tapering off process. Extension beyond these periods should not take place without re-evaluation of the situation.

It may be useful to inform the patient when treatment is started that it will be of limited duration and to explain precisely how the dosage will be progressively decreased. Moreover it is important that the patient should be aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms should they occur while the medicinal product is being discontinued. There are indications, that in the case of benzodiazepines with a short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high. When benzodiazepines with a long duration of action are being used it is important to warn against changing to a benzodiazepine with a short duration of action, as withdrawal symptoms may develop.

### *Amnesia*

Benzodiazepines may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product and therefore to reduce the risk patients should ensure that they will be able to have uninterrupted sleep of 7-8 hours (see section 4.8).

### *Psychiatric and paradoxical reactions*

Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepines. Should this occur, use of the medicinal product should be discontinued. They are more likely to occur in children and the elderly.

### *Tolerance*

Some loss of efficacy to the hypnotic effects of benzodiazepines may develop after repeated use for a few weeks.

Episodes of hypomania and mania have been reported in association with the use of alprazolam in patients with depression.

Benzodiazepines are not recommended for the primary treatment of psychotic illness.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

## **4.5 Interaction with other medicinal products and other forms of interaction**

### *Opioids*

The concomitant use of sedative medicines such as benzodiazepines or related drugs such as ANAXAL with opioids increases the risk of sedation, respiratory depression, coma and death because of additive central nervous system (CNS) depressant effect. The dosage and duration of concomitant use should be limited (see section 4.4). Concomitant intake with alcohol is not recommended. Alprazolam should be used with caution when combined with CNS depressants. Enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, anti-epileptic drugs, anaesthetics and sedative antihistamines. In the case of narcotic analgesics enhancement of the euphoria may also occur leading to an increase in psychic dependence.

Pharmacokinetic interactions can occur when alprazolam is administered along with drugs that interfere with its metabolism.

### *CYP3A Inhibitors*

Compounds that inhibit certain hepatic enzymes (particularly cytochrome P450 3A4) may increase the concentration of alprazolam and enhance its activity. Data from clinical studies with alprazolam, in-vitro studies with alprazolam and clinical studies with drugs metabolised similarly to alprazolam provide evidence for varying degrees of interaction and possible interaction with alprazolam for a number of drugs. Based on the degree of interaction and the type of data available, the following recommendations are made:

- The co-administration of alprazolam with ketoconazole, itraconazole, or other azole-type antifungals is not recommended.
- The co-administration of nefazodone or fluvoxamine increases the AUC of alprazolam by approximately 2-fold. Caution and consideration of dose reduction is recommended when alprazolam is co-administered with nefazodone, fluvoxamine and cimetidine.

- Caution is recommended when alprazolam is co-administered with fluoxetine, propoxyphene, oral contraceptives, sertraline, diltiazem, or macrolide antibiotics such as erythromycin, clarithromycin and troleandomycin.

#### *CYP3A4 Inducers*

Since alprazolam is metabolized by CYP3A4, inducers of this enzyme may enhance the metabolism of alprazolam. Interactions involving HIV protease inhibitors (e.g. ritonavir) and alprazolam are complex and time dependent. Short term, low doses of ritonavir resulted in a large impairment of alprazolam clearance, prolonged its elimination half-life and enhanced clinical effects. However, upon extended exposure to ritonavir, CYP3A induction offset this inhibition. This interaction will require a dose-adjustment or discontinuation of alprazolam.

#### *Digoxin*

Increased digoxin concentrations have been reported when alprazolam was given, especially in elderly (>65 years of age). Patients who receive alprazolam and digoxin should therefore be monitored for signs and symptoms related to digoxin toxicity.

### **4.6 Fertility, pregnancy and lactation**

#### Pregnancy

The data concerning teratogenicity and effects on postnatal development and behavior following benzodiazepine treatment are inconsistent. A large amount of data based on cohort studies indicate that first trimester exposure to benzodiazepine is not associated with an increase in the risk of major malformation. However, some early case-control epidemiological studies have found a twofold increased risk of oral clefts.

Benzodiazepine treatment at high dose, during the second and/or the third trimester of pregnancy, has revealed a decrease of fetal active movements and a variability of fetal cardiac rhythm.

When treatment has to be administered for medical reasons during the last part of pregnancy, even at low doses, floppy infant syndrome such as axial hypotonia, sucking troubles leading to a poor weight gain may be observed. These signs are reversible but they may last from 1 up to 3 weeks, according to the half-life of the product. At high doses, respiratory depression or apnoea and hypothermia in newborn may appear. Moreover, neonatal withdrawal symptoms with hyper excitability, agitation and tremor may be observed a few days after birth, even if no floppy infant syndrome is observed. The apparition of withdrawal symptoms after birth depends on the half-life of the substance.

Alprazolam should not be used during pregnancy unless the clinical condition of the woman requires treatment with alprazolam. If alprazolam is used during pregnancy, or of the patient becomes pregnant while taking alprazolam, the patient should be apprised of the potential hazard to the fetus.

If alprazolam treatment is necessary during last part of pregnancy, high doses should be avoided and withdrawal symptoms and/or floppy infant syndrome should be monitored in newborn.

#### Breast-feeding

Alprazolam is excreted in breast milk at low level. However, alprazolam is not recommended during breast-feeding.

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

Sedation, amnesia, impaired concentration and impaired muscle function may adversely affect the ability to drive and use machines. If insufficient sleep occurs, the likelihood of impaired alertness may be increased (see section 4.5).

These effects are potentiated by alcohol (see section 4.5).

Patients should be cautioned about operating motor vehicles or engaging in other dangerous activities while taking ANAXAL.

This medicine can impair cognitive function and can affect a patient's ability to drive safely.

When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
  - The medicine has been prescribed to treat a medical or dental problem and
  - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
  - It was not affecting your ability to drive safely

#### 4.8 Undesirable effects

Adverse events, if they occur, are generally observed at the beginning of therapy and usually disappear upon continued medication or decreased dosage.

The following undesirable effects have been observed and reported during treatment with alprazolam with the following frequencies: Very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ), not known (cannot be estimated from the available data).

<b>MedDRA System Organ Class</b>	<b>Frequency</b>	<b>Undesirable Effects</b>
<b>Endocrine disorders</b>	<b>Not known</b>	Hyperprolactinaemia*
<b>Metabolism and nutrition disorders</b>	<b>Common</b>	Decreased appetite
<b>Psychiatric disorders</b>	<b>Very common</b>	Depression
	<b>Common</b>	Confusional state, disorientation, libido decreased, anxiety, insomnia, nervousness, libido increased*
	<b>Uncommon</b>	Mania* (see section 4.4), hallucination*, anger*, agitation*
	<b>Not known</b>	Hypomania*, aggression*, hostility*, thinking abnormal*, psychomotor hyperactivity*
<b>Nervous system disorders</b>	<b>Very common</b>	Sedation, somnolence, ataxia, memory impairment, dysarthria, dizziness, headache
	<b>Common</b>	Balance disorder, coordination abnormal, disturbance in attention, hypersomnia, lethargy, tremor

	<b>Uncommon</b>	Amnesia
	<b>Not Known</b>	Autonomic nervous system imbalance*, dystonia*
<b>Eye disorders</b>	<b>Common</b>	Vision blurred
<b>Gastrointestinal disorders</b>	<b>Very common</b>	Constipation, dry mouth
	<b>Common</b>	Nausea
	<b>Not known</b>	Gastrointestinal disorder*
<b>Hepatobiliary disorders</b>	<b>Not known</b>	Hepatitis*, hepatic function abnormal*, jaundice*
<b>Skin and subcutaneous tissue disorders</b>	<b>Common</b>	Dermatitis*
	<b>Not Known</b>	Angioedema*, photosensitivity reaction*
<b>Musculoskeletal and connective tissue disorders</b>	<b>Uncommon</b>	Muscular weakness
<b>Renal and urinary disorders</b>	<b>Uncommon</b>	Incontinence*
	<b>Not known</b>	Urinary retention*
<b>Reproductive system and breast disorders</b>	<b>Common</b>	Sexual dysfunction*
	<b>Uncommon</b>	Menstruation irregular*
<b>General disorders and administration site conditions</b>	<b>Very common</b>	Fatigue, irritability
	<b>Not Known</b>	Oedema peripheral*
<b>Investigations</b>	<b>Common</b>	Weight increased, weight decreased
	<b>Not known</b>	Intraocular pressure increased*

\* ADR identified post-marketing

Withdrawal symptoms have occurred following rapid decrease or abrupt discontinuance of benzodiazepines including alprazolam. These can range from mild dysphoria and insomnia to a major syndrome, which may include abdominal and muscle cramps, vomiting, sweating, tremor and convulsions. In addition, withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy with alprazolam.

#### *Amnesia*

Anterograde amnesia may occur at therapeutic dosages, the risk increasing at higher dosages. Amnesic effects may be associated with inappropriate behaviour (see section 4.4).

#### *Depression*

Pre-existing depression may be unmasked during benzodiazepine use.

#### *Psychiatric and paradoxical reactions*

Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepines or benzodiazepine-like agents. They may be quite severe with this product. They are more likely to occur in children and the elderly.

In many of the spontaneous case reports of adverse behavioural effects, patients were receiving other CNS drugs concomitantly and/or were described as having underlying psychiatric conditions. Patients who have borderline personality disorder, a prior history of violent or

aggressive behaviour, or alcohol or substance abuse may be at risk of such events. Instances of irritability, hostility and intrusive thoughts have been reported during discontinuance of alprazolam in patients with post-traumatic stress disorder.

#### *Dependence*

Use (even at therapeutic doses) may lead to the development of physical dependence: discontinuation of the therapy may result in withdrawal or rebound phenomena (see section 4.4). Psychic dependence may occur. Abuse of benzodiazepines has been reported.

#### Reporting of 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.

### **4.9 Overdose**

As with other benzodiazepines, overdose should not present a threat to life unless combined with other CNS depressants (including alcohol). In the management of overdose with any medicinal product, it should be borne in mind that multiple agents have been taken.

Following overdose with oral benzodiazepines, vomiting may be induced (within 1 hour) if the patient is conscious or gastric lavage undertaken with the airway protected if the patient is unconscious. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption.

Special attention should be paid to respiratory and cardiovascular functions in intensive care.

Overdose of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion and lethargy, in more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, rarely coma and very rarely death.

Flumazenil may be useful as an antidote.

## **5. Pharmacological properties**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Benzodiazepine derivatives, ATC code: N05BA12

Alprazolam, like other benzodiazepines, has a high affinity for the benzodiazepine binding site in the brain. It facilitates the inhibitory neurotransmitter action of gamma-aminobutyric acid, which mediates both pre- and post synaptic inhibition in the central nervous system (CNS).

### **5.2 Pharmacokinetic properties**

Alprazolam is readily absorbed. Following oral administration peak concentration in the plasma occurs after 1 - 2 hours.

The mean half-life is 12 - 15 hours. Repeated dosage may lead to accumulation and this should be borne in mind in elderly patients and those with impaired renal or hepatic function.

Alprazolam and its metabolites are excreted primarily in the urine.

*In vitro* alprazolam is bound (80%) to human serum protein.

### **5.3 Preclinical safety data**

#### Mutagenesis and Carcinogenesis

Non-clinical data reveal no special hazard for humans based on conventional studies of genotoxicity and carcinogenic potential.



### Ocular Effects

When rats were treated orally with alprazolam for 2 years, a tendency for a dose related increase in the number of cataracts (females) and corneal vascularization (males) was observed. These lesions did not appear until after 11 months of treatment.

### Fertility

In reproductive toxicity studies administration of alprazolam in rats and rabbits is associated at very high doses with developmental delay and an increased incidence of fetal death and skeletal malformations. In fertility studies, treatment of male rats at high doses prior to mating resulted in a decrease in the percentage of dams conceiving.

### Effect of anesthetic and sedative drugs

Nonclinical research has shown that administration of anesthetic and sedation drugs that block N-methyl-D-aspartate (NMDA) receptors and/or potentiate gamma-aminobutyric acid (GABA) activity can increase neuronal cell death in the brain and result in long term deficits in cognition and behavior of juvenile animals when administered during the period of peak brain development. Based on comparisons across nonclinical species, the window of vulnerability of the brain to these effects is believed to correlate with human exposures in the third trimester of pregnancy through the first year of life, but may extend to approximately 3 years of age. While there is limited information of this effect with alprazolam, since the mechanism of action includes potentiation of GABA activity, a similar effect may occur. The relevance of these nonclinical findings to human use is unknown.

## **6. Pharmaceutical particulars**

### **6.1 List of excipients**

- Lactose monohydrate
- Cellulose microcrystalline
- DSS 85%
- pregelatinized starch
- crospovidone
- colloidal silicon dioxide
- magnesium stearate.

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years.

#### **6.4 Special precautions for storage**

Do not store above 25°C.

Store in the original package in order to protect from moisture.

#### **6.5 Nature and contents of container**

Box of 30 tablets (equal, rounded, slightly biconvex tablets, white , with brake line on one side) of 0,25 mg alprazolam u blister pack.

Box of 30 tablets (equal, rounded, slightly biconvex tablets, light pink , with brake line on one side) of 0,5 mg alprazolam u blister pack.

Box of 30 tablets (equal, rounded, slightly biconvex tablets, light blue , with brake line on one side) of 1 mg alprazolam u blister pack.

#### **6.6 Special precautions for disposal and other handling**

No special requirements for disposal.

#### **7. Marketing authorisation holder**

ZADA Pharmacauticals Ltd.

Donji Bistarac without number

75 300 Lukavac

Bosnia and Herzegovina

#### **8. Marketing authorisation number(s)**

Δ ANAXAL, tablet, 30x0,25 mg: 04-07.3-2-2406/16

Δ ANAXAL, tablet, 30x0,5 mg: 04-07.3-2-2407/16

Δ ANAXAL, tablet, 30x1 mg: 04-07.3-2-2408/16

#### **9. Date of first authorisation/renewal of the authorisation**

Δ ANAXAL, tableta, 30x0,25 mg: 02.03.2017.

Δ ANAXAL, tableta, 30x0,5 mg: 02.03.2017.

Δ ANAXAL, tableta, 30x1 mg: 02.03.2017.

#### **10. Date of revision of the text**

01/2019