SUMMARY OF THE PRODUCT CHARACTERISTICS

1. TRADE NAME OF THE MEDICINAL PRODUCT

TRANXAL 5 mg, hard capsules
TRANXAL 15 mg, hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

Tranxal 5 mg
Clorazepate dipotassium 5mg

Tranxal 15 mg
Clorazepate dipotassium 15mg

3.. PHARMACEUTICAL FORM

Capsules

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the management and relief of anxiety, symptomatic relief of acute alcohol withdrawal, adjunctive therapy in the management of partial seizures.

4.2 Posology and route of administration

Duration:
Treatment should be as of a short duration as possible and reassessed on a regular basis, particularly if the patient has no symptoms. The overall duration of treatment should not exceed 8 to 12 weeks in most of patients, including the period of dosage tapering (see section 4.4 special warnings and special precautions for use).
In some cases, it may be necessary to prolong treatment beyond the recommended period. Prolonged treatment requires careful and repeated assessments of the patient's status.

Prevention and treatment of delirium tremens and other symptoms of alcohol withdrawal: short-term treatment of about 8 to 10 days.

Dose:
In all cases, treatment must be initiated at the lowest effective dose, and the maximum dose of 90 mg per day in adults must not be exceeded.

This medication is reserved for use in adults and children over 6 years of age.

The usual dosage in adults is 5 to 30 mg per day for the 5 mg capsule and 25 to 90 for the 15 mg capsule.

In children: use must be exceptional and the dosage is about 0.5 mg/kg/day divided into several doses.

In elderly subjects or subjects with renal or hepatic insufficiency :dosage reduction recommended, by half for example.

Methods for cessation of treatment: treatment should be stopped gradually with decreasing dosage over several weeks (see Precautions for use).

4.3 Contraindications

This medication must never be used in the following cases:
- known hypersensitivity to the active substance or one of the other ingredients
- severe respiratory insufficiency
- sleep apnea syndrome
- severe, acute or chronic hepatic insufficiency (risk of onset of encephalopathy)
- myasthenia gravis
- breast-feeding
- as well as in combination with alcohol

4.4 Special warnings and special precautions for use

Special Warning

PHARMACOLOGICAL TOLERANCE:

The anxiolytic effect of benzodiazepines and related substances may gradually decline, despite using the same dose, if administrated over a period of several weeks.

DEPENDENCE:

Any treatment with benzodiazepines and related substances, and particularly in the event of prolonged use, may cause a physical and psychological state of drug dependence.

A variety of factors seem to favor the onset of dependence:

- duration of treatment
- dose
- history of medicinal or other dependencies, including alcohol

Drug dependence may occur at therapeutic doses and/or in patients without a specific risk factor.

This state may cause a withdrawal syndrome on treatment discontinuation.
Some symptoms are frequent and seem to be common: insomnia, headache, severe anxiety, myalgia, muscular tension, irritability.
Other symptoms are more rare: agitation or even episodes of confusion, paresthesia of the extremities, hyper-reactivity to light, noise or physical contact , de-personalization, de-realization, hallucinations, seizure.
Withdrawal symptoms may occur during the days following treatment discontinuation.
For benzodiazepines with a short duration of action, and particularly if they are given at high doses, the symptoms may even appear during the interval between two doses; this has not been observed with dipotassium clorazepate because of its long half-life (see section 5.2 Pharmacokinetic properties).
Regardless of the indication, i.e. anxiety or sleep disorder, the combination use of several benzodiazepines may increase the risk of drug dependence.
Cases of abuse have also been reported.

Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including TRANXAL, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.
Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to

placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed. Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table1: Risk by indication for antiepileptic drugs in the pooled analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing TRANXAL or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

REBOUND EFFECT:

This transient syndrome may appear as an exacerbation of the anxiety which was the original reason for treatment with benzodiazepines or related substances.

AMNESIA AND PSYCHOMOTOR FUNCTION DISORDERS:

Anterograde amnesia and psychomotor function disorders may occur during the hours following administration.

BEHAVIORAL DISORDERS:
In some subjects, benzodiazepines and related substances may cause a syndrome involving different degrees of impaired consciousness with behavioral and memory disorders.
- worsening of insomnia, nightmares, agitation, nervousness,
- delusions, hallucinations, confusion and onirism, psychotic-type symptoms,
- loss of inhibition with impulsiveness,
- euphoria, irritability,
- anterograde amnesia,
- suggestibility

This syndrome may be accompanied by disorders potentially dangerous to the patient or to others, such as:
- unusual behaviour of the patient,
- self-aggression or aggression towards others, particularly if family and friends try to prevent the patient from doing what he/she wants,
- automatic behaviour with post-event amnesia.

These symptoms require treatment discontinuation.

RISK OF ACCUMULATION
Benzodiazepines and related substances (like all medicinal products) remain in the body for a period of about 5 half-lives (see section Pharmacokinetic properties).
In the elderly or those suffering from renal or hepatic insufficiency, the half-life may be considerably prolonged. In the event of repeated doses, the medicinal product or its metabolites reach the steady-state plateau much later and at a much higher level. It is only after the steady-state plateau has been reached that it is possible to assess both the efficacy and the safety of the drug.
Dose adjustment may be necessary (see section Posology and method of administration).

ELDERLY SUBJECTS
Benzodiazepines and related substances should be used with care in elderly subjects, because of the risk of sedation and/or muscle-relaxant effects which may promote falls, with implications which are often serious in this population.

Precautions for use

Extreme caution is recommended in patients with a history of alcoholism or other dependencies, whether drug-related or not (see section 4.5 interaction with other medical products and other forms of interaction).

SUBJECTS WITH A MAJOR DEPRESSIVE EPISODE

Benzodiazepines and related substances should not be prescribed alone, since the depression continues to develop independently, with persistent or enhanced risk of suicide.

METHODS FOR THE GRADUAL DISCONTINUATION OF TREATMENT:

These methods should be explained in detail to the patient.
In addition to the need to gradually taper the doses, patients should be warned of the possibility of a rebound effect, so as to minimize any anxiety which may arise because of the symptoms resulting from discontinuation, even if gradual.

The patient should be warned that these treatment phase may be unpleasant.

CHILDREN:

Even more than in adults, the benefit/risk ratio should be scrupulously evaluated and treatment duration should be as short as possible.

ELDERLY SUBJECTS, PATIENTS WITH RENAL OR HEPATIC INSUFFICIENCY:

The risk of accumulation require dose reduction by half for example (see Special warnings).

RESPIRATORY INSUFFICIENCY:

In patients with respiratory insufficiency, the depressant effect of benzodiazepines and related substances should be taken into account (particularly since anxiety and agitation may constitute warning signs of decompensation of respiratory function, which justifies transfer to an intensive care unit).

4.5 Interactions with other medicaments and other forms of interaction

Inadvisable combinations:

+ Alcohol
Alcohol enhances the sedative effect of benzodiazepines and related substances . Impaired alertness may render driving or machines operation dangerous.
Avoid the consumption of alcoholic drinks or medicinal products containing alcohol.

Combinations to be taken into account:

+ Other CNS depressant drugs including **sedatives :** morphine derivatives (analgesics, antitussives and replacement therapies other than buprenorphine ; neuroleptics, barbiturates, other anxiolytics; hypnotics, sedative antidepressants, sedative H1 anti-histamines, centrally-acting anti-hypertensives, baclofene, thalidomide, pizotifen.
Increased central depression . Impaired alertness may render driving or machines operation dangerous.
In addition, for morphine derivatives (analgesics, antitussives and replacement therapies), barbiturates: increased risk of respiratory depression, which may be fatal in the event of an overdose.

+ Buprenorphine
Increase risk of respiratory depression, which may be fatal.

The benefit/risk ratio of this combination should be assessed with care. The patient must be informed of the need to comply with the doses prescribed.

+ Clozapine
Risk of circulatory collapse with respiratory or cardiac arrest is enhanced.

4.6 Pregnancy and lactation

Pregnancy

An increased risk of congenital malformations associated with the use of minor tranquilizers (chlordiazepoxide, diazepam, and meprobamate) during the first trimester of pregnancy has been suggested in several studies. Clorazepate dipotassium, a benzodiazepine derivative, has not been studied adequately to determine whether it, too, may be associated with an increased risk of fetal abnormality. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. Patients should be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physician about the desirability of discontinuing the drug.

Lactation

TRANXAL tablets should not be given to nursing mothers since it has been reported that nordiazepam is excreted in human breast milk

4.7 Effects on ability to drive and use machines

Drivers and machine operators should be warned of the possible risk of drowsiness.

Combination use with other sedative medicinal products is inadvisable or must be taken into account in the event of driving or using machines (see section 4.5 interaction with other medicinal products and other forms of interaction .

If the sleep duration is insufficient, the risk of impaired alertness is further enhanced.

4.8 Undesirable effects

These are related to the dose ingested and the individual sensitivity of the patient.

Neurological and psychiatric undesirable effects (see section 4.4 Special warnings and special precautions for use)

- anterograde amnesia, which may occur at therapeutic doses, the risk increasing proportionally with the dose,
- behavioral disorders, impaired consciousness, irritability, aggressiveness, agitation,
- physical or psychological dependence, even at therapeutic doses, with a withdrawal syndrome or rebound phenomenon at treatment discontinuation.
- sensations of drunkenness, headaches, ataxia,
- confusion, impaired alertness or even drowsiness, (particularly in elderly subjects), insomnia, nightmares, tension.
- changes in libido.

Cutaneous undesirable effects

- skin rashes, pruriginous or not.

Systemic undesirable effects

- muscular hypotonia, asthenia

Ocular undesirable effects

- diplopia

Also:
- allergic reactions such as erythema, pruritus, urticaria, or angioedema,
- rare cases of polymorphous erythema,
- very rare cases of Stevens Johnson syndrome and Lyell's syndrome. These reactions have occurred with combination use with medications known to induce such events.

4.9 Overdose

Overdose may be life-threatening, particularly in cases of multiple intoxication involving other central nervous system depressants (including alcohol).

In the event of a massive overdose, the main sign is CNS depression, which may range from drowsiness to coma, depending on the quantity ingested.
Benign overdoses are characterized by signs of mental confusion or lethargy.
The more serious cases are characterized by ataxia, hypotonia, hypotension, respiratory depression and exceptionally death.
In the event of an oral overdose within the past hour vomiting should be induced if the patient is conscious, or if not, gastric lavage performed with protection of the airways.
Beyond this period, the administration of activated charcoal may reduce absorption .
Close monitoring of the cardiac and respiratory functions in a specialized unit is recommended.

The administration of flumazenil may be useful for diagnosis and/or treatment of an intentional or accidental overdose with benzodiazepines.
Flumazenil antagonism of the benzodiazepine effect may favor the onset of neurological disorders (convulsions), particularly in epileptic patients.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ANXIOLYTICS

ATC Code: N05BA 05
(N: central nervous system)

Clorazepate belongs to the class of 1-4 benzodiazepines and has a pharmacodynamic effect which is qualitatively similar to that of other compounds in that class:

- muscle relaxant,
- anxiolytic,
- sedative,
- hypnotic,
- anticonvulsant,
- amnesic

These effects are related to a specific agonist action on a central receptor belonging to the "GABA-OMEGA macromolecular receptors" complex, also referred to as BZ_1 and BZ_2 which modulate the opening of the chlorine channel.

5.2 Pharmacokinetic properties

Absorption
Most (80%) of the clorazepate is rapidly decarboxylated in the stomach to produce desmethyldiazepam, peak plasma levels of which are reached in about 1 hour (Tmax=1 hour).

Distribution
The distribution volume of of desmethyldiazepam is about 1 l/kg.
Protein binding is marked, greater than 97%.
It has not been possible to establish a concentration-effect relationship for this class of products, because of the intensity of their metabolism and the development of tolerance.
Benzodiazepines cross the blood-brain barrier, as well as into the placenta and breast milk.

Metabolism and elimination
The principal metabolite of clorazepate is desmethyldiazepam, which is also active and has a longer half-life than the parent compound (between 30 to 150 hours).
Hydroxylation of this compound gives rise to another active metabolite, oxazepam.
It is inactivated by glucuronide conjugation, producing water soluble substances which are excreted in the urine.

Population at risk:

Elderly subjects:
Hepatic metabolism decline, decreases as does total clearance,
with increased concentrations at the steady state, free fraction and the half-lives.
It is important to reduce the dosage.

Patients with hepatic insufficiency:
A lengthening of the half-life is observed, with a reduction in total plasma clearance.

6. PHARMACEUTICAL DATA

6.1 Special precautions for storage

Tranxal capsules must be kept at room temperature, in a dry place and protected from light.

6.2 Other ingredients:

Tranxal 5 mg
Purified Talc, Gelatin, Potassium Carbonate, Titanium Oxide, Titanium Dioxide, Erythrosin, Quinoline Yellow.

Tranxal 15 mg
Purified Talc, Gelatin, Potassium Carbonate, Titanium Oxide, Titanium Dioxide, Erythrosin, Indigo Carmine.

6.3 Nature and contents of container: Glass jars: 30 capsules

7. Manufacturer: CTS Chemical Industries Ltd, Kiryat Malachi

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