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

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS
• Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death *[*see *chapter* **Drug Interactions***]*. • Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. • Limit dosages and durations to the minimum required. • Follow patients for signs and symptoms of respiratory depression and sedation.

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 sections WARNINGS and PRECAUTIONS).
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.

Pediatric population

Tranxal is not indicated for the management of partial seizures in pediatric patients under 9 years old.
Tranxal is not indicated for the management and relief of anxiety and symptomatic relief of acute alcohol withdrawal in pediatric patients under 6 years old.

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.

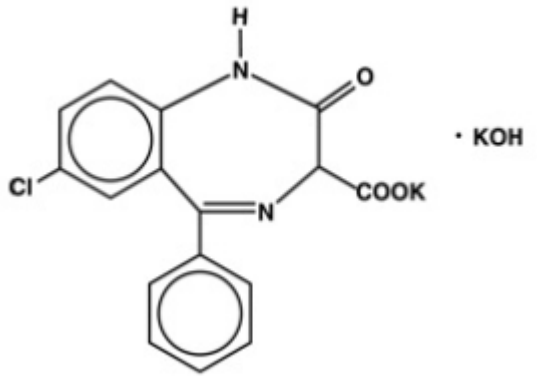
The usual dosage in adults is 5 to 30 mg per day for the 5 mg capsule and 25 to 90 for the 15 mg capsule.

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 WARNINGS).

DESCRIPTION
Chemically, clorazepate dipotassium is a benzodiazepine. The molecular formula is $C_{16}H_{11}ClK_2N_2O_4$;
the molecular weight is 408.92; 1*H*-1,4-Benzodiazepine-3-carboxylic acid, 7-chloro-2,3-dihydro-2-oxo-5-phenyl-, potassium salt compound with potassium hydroxide (1:1) and the structural formula may be represented as follows:



The compound occurs as a fine, light yellow, practically odorless powder. It is insoluble in the common organic solvents, but very soluble in water. Aqueous solutions are unstable, clear, light yellow, and alkaline.

CLINICAL PHARMACOLOGY

Pharmacologically, clorazepate dipotassium has the characteristics of the benzodiazepines. It has depressant effects on the central nervous system. The primary metabolite, nordiazepam, quickly appears in the blood stream. The serum half-life is about 2 days. The drug is metabolized in the liver and excreted primarily in the urine.

Studies in healthy men have shown that clorazepate dipotassium has depressant effects on the central nervous system. Prolonged administration of single daily doses as high as 120 mg was without toxic effects. Abrupt cessation of high doses was followed in some patients by nervousness, insomnia, irritability, diarrhea, muscle aches, or memory impairment.

Since orally administered clorazepate dipotassium is rapidly decarboxylated to form nordiazepam, there is essentially no circulating parent drug. Nordiazepam, the primary metabolite, quickly appears in the blood and is eliminated from the plasma with an apparent half-life of about 40 to 50 hours. Plasma levels of nordiazepam increase proportionally with clorazepate dipotassium dose and show moderate accumulation with repeated administration. The protein binding of nordiazepam in plasma is high (97-98%).

Within 10 days after oral administration of a 15 mg (50 µCi) dose of C-clorazepate dipotassium to two volunteers, 62-67% of the radioactivity was excreted in the urine and 15-19% was eliminated in the feces. Both subjects were still excreting measurable amounts of radioactivity in the urine (about 1% of the C-dose) on day ten. Nordiazepam is further metabolized by hydroxylation. The major urinary metabolite is conjugated oxazepam (3-hydroxynordiazepam), and smaller amounts of conjugated p-hydroxynordiazepam and nordiazepam are also found in the urine.

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Patients with acute narrow angle glaucoma.

WARNINGS

Risks from Concomitant Use with Opioids

Concomitant use of benzodiazepines, including clorazepate dipotassium, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. If a decision is made to prescribe clorazepate dipotassium concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of

respiratory depression and sedation. In patients already receiving an opioid analgesic, prescribe a lower initial dose of clorazepate dipotassium than indicated in the absence of an opioid and titrate based on clinical response. If an opioid is initiated in a patient already taking clorazepate dipotassium, prescribe a lower initial dose of the opioid and titrate based upon clinical response.
Advise both patients and caregivers about the risks of respiratory depression and sedation when clorazepate dipotassium are used with opioids. Advise patients not to drive or operate heavy machinery until the effects of concomitant use with the opioid have been determined (see DRUG INTERACTIONS).

Use in Depressive Neuroses or Psychotic Reactions
Clorazepate dipotassium are not recommended for use in depressive neuroses or in psychotic reactions.

Use in Children
This medication is reserved for use in adults and children over 6 years of age.
Interference with Psychomotor Performance
Patients taking clorazepate dipotassium should be cautioned against engaging in hazardous occupations requiring mental alertness, such as operating dangerous machinery including motor vehicles.

Concomitant Use with CNS Depressants
Since clorazepate dipotassium has a central nervous system depressant effect, patients should be advised against the simultaneous use of other CNS depressant drugs, and cautioned that the effects of alcohol may be increased.

Physical and Psychological Dependence
Withdrawal symptoms (similar in character to those noted with barbiturates and alcohol) have occurred following abrupt discontinuance of clorazepate. Withdrawal symptoms associated with the abrupt discontinuation of benzodiazepines have included convulsions, delirium, tremor, abdominal and muscle cramps, vomiting, sweating, nervousness, insomnia, irritability, diarrhea, and memory impairment. The more severe withdrawal symptoms have usually been limited to those patients who had received excessive doses over an extended period of time. Generally milder withdrawal symptoms have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months. Consequently, after extended therapy, abrupt discontinuation of clorazepate should generally be avoided and a gradual dosage tapering schedule followed.
Caution should be observed in patients who are considered to have a psychological potential for drug dependence.
Evidence of drug dependence has been observed in dogs and rabbits which was characterized by convulsive seizures when the drug was abruptly withdrawn or the dose was reduced; the syndrome in dogs could be abolished by administration of clorazepate.

Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including clorazepate dipotassium, 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.

Table 1: 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 clorazepate dipotassium 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.

Usage in 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.

Usage during Lactation
Clorazepate dipotassium should not be given to nursing mothers since it has been reported that nordiazepam is excreted in human breast milk.

PRECAUTIONS
In those patients in which a degree of depression accompanies the anxiety, suicidal tendencies may be present and protective measures may be required. The least amount of drug that is feasible should be available to the patient.
Patients taking clorazepate dipotassium for prolonged periods should have blood counts and liver function tests periodically. The usual precautions in treating patients with impaired renal or hepatic function should also be observed.
In elderly or debilitated patients, the initial dose should be small, and increments should be made gradually, in accordance with the response of the patient, to preclude ataxia or excessive sedation.

Information for Patients
To assure the safe and effective use of benzodiazepines, patients should be informed that, since benzodiazepines may produce psychological and physical dependence, it is essential that they consult with their physician before either increasing the dose or abruptly discontinuing this drug.
Patients, their caregivers, and families should be counseled that AEDs, including clorazepate dipotassium, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of

symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with clorazepate dipotassium and should counsel them in its appropriate use.

Pediatric Use
See WARNINGS.

Geriatric Use
Clinical studies of clorazepate dipotassium were not adequate to determine whether subjects aged 65 and over respond differently than younger subjects. Elderly or debilitated patients may be especially sensitive to the effects of all benzodiazepines, including clorazepate dipotassium. In general, elderly or debilitated patients should be started on lower doses of clorazepate dipotassium and observed closely, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and concomitant disease or other drug therapy. Dose adjustments should also be made slowly, and with more caution in this patient population (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS
The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at GABAA sites and opioids interact primarily at mu receptors. When benzodiazepines and opioids are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists. Limit dosage and duration of concomitant use of benzodiazepines and opioids, and monitor patients closely for respiratory depression and sedation.
If clorazepate dipotassium are to be combined with other drugs acting on the central nervous system, careful consideration should be given to the pharmacology of the agents to be employed.
Animal experience indicates that clorazepate dipotassium prolongs the sleeping time after hexobarbital or after ethyl alcohol, increases the inhibitory effects of chlorpromazine, but does not exhibit monoamine oxidase inhibition. Clinical studies have shown increased sedation with concurrent hypnotic medications. The actions of the benzodiazepines may be potentiated by barbiturates, narcotics, phenothiazines, monoamine oxidase inhibitors or other antidepressants.
If clorazepate dipotassium are used to treat anxiety associated with somatic disease states, careful attention must be paid to possible drug interaction with concomitant medication.
In bioavailability studies with normal subjects, the concurrent administration of antacids at therapeutic levels did not significantly influence the bioavailability of clorazepate dipotassium.

ADVERSE REACTIONS

The side effect most frequently reported was drowsiness. Less commonly reported (in descending order of occurrence) were: dizziness, various gastrointestinal complaints, nervousness, blurred vision, dry mouth, headache, and mental confusion. Other side effects included insomnia, transient skin rashes, fatigue, ataxia, genitourinary complaints, irritability, diplopia, depression, tremor, and slurred speech.
There have been reports of abnormal liver and kidney function tests and of decrease in hematocrit.
Decrease in systolic blood pressure has been observed.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

OVERDOSAGE

Overdosage is usually manifested by varying degrees of CNS depression ranging from slight sedation to coma. As in the management of overdosage with any drug, it should be borne in mind that multiple agents may have been taken.
The treatment of overdosage should consist of the general measures employed in the management of overdosage of any CNS depressant. Gastric evacuation either by the induction of emesis, lavage, or both, should be performed immediately. General supportive care, including frequent monitoring of the vital signs and close observation of the patient, is indicated. Hypotension, though rarely reported, may occur with large overdoses. In such cases the use of agents such as norepinephrine bitartrate injection, USP or metaraminol bitartrate injection, USP should be considered.
While reports indicate that individuals have survived overdoses of clorazepate dipotassium as high as 450 to 675 mg, these doses are not necessarily an accurate indication of the amount of drug absorbed since the time interval between ingestion and the institution of treatment was not always known. Sedation in varying degrees was the most common physiological manifestation of clorazepate dipotassium overdosage. Deep coma when it occurred was usually associated with the ingestion of other drugs in addition to clorazepate dipotassium Flumazenil, a specific benzodiazepine receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with a benzodiazepine is known or suspected. Prior to the administration of flumazenil, necessary measures should be instituted to secure airway, ventilation, and intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for resedation, respiratory depression, and other residual benzodiazepine effects for an appropriate period after treatment. **The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose.** The complete flumazenil package insert including

CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS should be consulted prior to use.

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 activity that is similar in qualitative terms to that of the 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 known as BZ1 and BZ2 modulating the opening of the chlorine ion channel.

ANIMAL PHARMACOLOGY AND TOXICOLOGY

Studies in rats and monkeys have shown a substantial difference between doses producing tranquilizing, sedative and toxic effects. In rats, conditioned avoidance response was inhibited at an oral dose of 10 mg/kg; sedation was induced at 32 mg/kg; the LD was 1320 mg/kg. In monkeys aggressive behavior was reduced at an oral dose of 0.25 mg/kg; sedation (ataxia) was induced at 7.5 mg/kg; the LD could not be determined because of the emetic effect of large doses, but the LD exceeds 1600 mg/kg.

Twenty-four dogs were given clorazepate dipotassium orally in a 22-month toxicity study; doses up to 75 mg/kg were given. Drug-related changes occurred in the liver; weight was increased and cholestasis with minimal hepatocellular damage was found, but lobular architecture remained well preserved.

Eighteen rhesus monkeys were given oral doses of clorazepate dipotassium from 3 to 36 mg/kg daily for 52 weeks. All treated animals remained similar to control animals. Although total leucocyte count remained within normal limits it tended to fall in the female animals on the highest doses.

Examination of all organs revealed no alterations attributable to clorazepate dipotassium. There was no damage to liver function or structure.

Reproduction Studies

Standard fertility, reproduction, and teratology studies were conducted in rats and rabbits. Oral doses in rats up to 150 mg/kg and in rabbits up to 15 mg/kg produced no abnormalities in the fetuses. Clorazepate dipotassium did not alter the fertility

indices or reproductive capacity of adult animals. As expected, the sedative effect of high doses interfered with care of the young by their mothers (see WARNINGS: Usage in Pregnancy).

6. PHARMACEUTICAL DATA

6.1 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.

6.2 Special precautions for storage

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

Discard 2 months after opening.

The expiry date of the product is indicated on the packaging materials

6.3 Nature and contents of container:

Glass jars: 30 capsules

7. Manufacturer and Marketing Authorization Holder

CTS Chemical Industries Ltd, Israel

3 HAKIDMA ST., KIRYAT MALACHI 83057, ISRAEL

Revised in 05 2021 according to MOHs guidelines