1. NAME OF THE MEDICINAL PRODUCT
LORIVAN

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains lorazepam 1mg.

Excipient: each tablet contains approximately 85.5 mg lactose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Tablet

White, round, biconvex tablets, scored on one side.
The score line is not intended for breaking the tablet.

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS

Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma and death [see sections 4.4, 4.5].

- 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
Anxiety and tension

4.2 Posology and method of administration
Lorivan tablets are for oral administration only.

Treatment to be given under close medical supervision.
Dosage and duration of therapy should be individualised. The lowest effective dose should be prescribed for the shortest time possible. The risk of withdrawal and rebound phenomena is greater after abrupt discontinuation; therefore, the drug should be discontinued gradually for all patients (see section 4.4). Generally, the duration of treatment varies from a few days to 4 weeks including the tapering off process.
Chronic use is not recommended (little is known of the long term safety and efficacy; potential for dependence–see section 4.4). Extension of the treatment period should not take place without re-evaluation of the need for continued therapy.

Increases in the dosage of lorazepam should be made gradually to help avoid adverse effects. The evening dose should be increased before the daytime doses.

When treatment is started, the patient should be informed that:

• treatment will be of limited duration
• the dosage will be progressively decreased
• there is a possibility of rebound phenomena

Dosage:

Adults:

1-4 mg daily in divided doses.

Elderly and debilitated patients:

Elderly and debilitated patients may respond to lower doses and half the normal adult dose or less may be sufficient. This initial dose should be adjusted as needed and tolerated.

Children (under the age of 13 years):

Lorazepam is not intended for the treatment of children under the age of 13 years.

Patients with Renal or Hepatic impairment:

Lower doses may be sufficient in patients with impaired renal function or mild to moderate hepatic insufficiency (see section 4.4 Special Warnings and Special Precautions for Use). Use in patients with severe hepatic insufficiency is contraindicated (see section 4.3 Contraindications).

4.3 Contraindications

Hypersensitivity to Lorazepam, other benzodiazepines or to any other of the excipients listed in section 6.1.

Acute pulmonary insufficiency: respiratory depression; sleep apnoea (risk of further respiratory depression)

Severe respiratory insufficiency

Obsessional states (inadequate evidence of safety and efficacy)

Planning a pregnancy (see section 4.6)

Pregnancy (unless there are compelling reasons- see section 4.6)

Myasthenia gravis

Severe hepatic insufficiency (may precipitate encephalopathy)

Acute narrow-angle glaucoma.

Benzodiazepines should not be used alone in anxiety with depression (may precipitate suicide)

4.4 Special warnings and precautions for use

Use of benzodiazepines, including lorazepam, both used alone and in combination with other CNS depressants may lead to potentially fatal respiratory depression.

Severe anaphylactic/anaphylactoid reactions have been reported with the use of benzodiazepines. Cases of angioedema involving the tongue, glottis or larynx have been reported in patients after taking the first or subsequent doses of benzodiazepines. Some patients taking benzodiazepines have had additional symptoms such as dyspnoea, throat closing, or nausea and vomiting. Some patients have required medical therapy in the emergency department. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal. Patients who develop angioedema after treatment with a benzodiazepine should not be rechallenged with the drug.

Lorazepam should be used with caution in patients with compromised respiratory function (e.g., COPD).

Patients should be advised that since their tolerance for alcohol and other CNS depressants will be diminished in the presence of lorazepam, these substances should either be avoided or taken in reduced dosage.

Anxiety may be a symptom of several other disorders. The possibility should be considered that the complaint may be related to an underlying physical or psychiatric disorder for which there is more specific treatment.

Abuse of benzodiazepines has been reported, especially in patients with a history of drug and/or alcohol abuse.

Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Limit dosages and durations to the minimum required.

Tolerance

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

There is evidence that tolerance develops to the sedative effects of benzodiazepines.

Lorazepam may have abuse potential, especially in patients with a history of drug and/or alcohol abuse.

Dependence

The use of benzodiazepines may lead to physical and psychological dependence. The risk of dependence on lorazepam is low when used at the recommended dose and duration, but increases with higher doses and longer term use. The risk of dependence is further increased in patients with a history of alcoholism or drug abuse, or in patients with significant personality disorders. Therefore, use in individuals with a history of alcoholism or drug abuse should be avoided.

Dependence may lead to withdrawal symptoms, especially if treatment is discontinued abruptly. Therefore, **the drug should always be discontinued gradually**.

Withdrawal symptoms can appear following cessation of recommended doses after as little as one week of therapy. Abrupt termination of treatment may be accompanied by withdrawal symptoms.

It may be useful to inform the patient that treatment will be of limited duration and that it will be discontinued gradually. The patient should also be made aware of the possibility of "rebound" phenomena to minimize anxiety should they occur.

Symptoms reported following discontinuation of benzodiazepines include headaches, muscle pain, anxiety, tension, depression, insomnia, restlessness, dizziness, nausea, diarrhoea, loss of appetite, confusion, hallucinations/delirium, perceptual changes, irritability, dysphoria, convulsions/seizures, tremor, abdominal cramps, myalgia, agitation, palpitations, tachycardia, panic attacks, vertigo, hyperreflexia, short-term memory loss, hyperthermia, sweating, and the occurrence of "rebound" phenomena whereby the symptoms that led to treatment with benzodiazepines recur in an enhanced form. These symptoms may be difficult to distinguish from the original symptoms for which the drug was prescribed.

In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, tinnitus, numbness and tingling of the extremities, hypersensitivity to light, noise, and physical contact/perceptual changes, involuntary movements, vomiting, hallucinations, catatonia, convulsions. Convulsions/seizures may be more common in patients with preexisting seizure disorders or who are taking other drugs that lower the convulsive threshold such as antidepressants.

Duration

Treatment should be as short as possible. Generally, the duration of treatment varies from a few days to 4 weeks including the tapering off process.

It may be useful to inform the patient that treatment will be of limited duration and that it will be discontinued gradually. The patient should also be made aware of the possibility of "rebound" phenomena to minimize anxiety should they occur.

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

Transient anterograde amnesia or memory impairment has been reported in association with the use of benzodiazepines.

Psychiatric and paradoxical reactions

Paradoxical reactions have been occasionally reported during benzodiazepine use (see Undesirable Effects). Such reactions may be more likely to occur in children and the elderly. Should these occur, use of the drug should be discontinued.

Specific patient groups

Lorivan (lorazepam) is not recommended for use in patients with a primary depressive disorder or psychosis.
Lorivan is not intended for the primary treatment of psychotic illness or depressive disorders, and should not be used alone to treat depressed patients. The use of benzodiazepines may have a disinhibiting effect and may release suicidal tendencies in depressed patients. Therefore, large quantities of Lorivan should not be prescribed to these patients. The use of benzodiazepines in these patients should not be used without adequate antidepressant therapy.
Pre-existing depression may emerge or worsen during benzodiazepine use.

Patients with impaired renal function or mild to moderate hepatic insufficiency should be monitored frequently and have their dosage adjusted carefully according to patient response. Lower doses may be sufficient in these patients. The same precautions apply to elderly or debilitated patients and patients with chronic respiratory insufficiency.

As with all CNS-depressants, the use of benzodiazepines may precipitate encephalopathy in patients with severe hepatic insufficiency. Therefore, use in these patients is contraindicated.

Some patients taking benzodiazepines have developed a blood dyscrasia, and some have had elevations in liver enzymes. Periodic haematologic and liver-function assessments are recommended where repeated courses of treatment are considered clinically necessary.

Although hypotension has occurred only rarely, benzodiazepines should be administered with caution to patients in whom a drop in blood pressure might lead to cardiovascular or cerebrovascular complications. This is particularly important in elderly patients.

In patients where gastrointestinal or cardiovascular disorders coexist with anxiety, it should be noted that lorazepam has not been shown to be of significant benefit in treating the gastrointestinal or cardiovascular component.

Esophageal dilation occurred in rats treated with lorazepam for more than one year at 6 mg/kg/day. The no-effect dose was 1.25 mg/kg/day. The effect was reversible only when the treatment was withdrawn within two months of first observation of the phenomenon. The clinical significance of this is unknown. However, use of lorazepam for prolonged periods and in geriatric patients requires caution, and there should be frequent monitoring for symptoms of upper G.I. disease.

Safety and effectiveness of lorazepam in children of less than 12 years have not been established.

Geriatric Use
Clinical studies of lorazepam generally were not adequate to determine whether subjects aged 65 and over respond differently than younger subjects; however, the incidence of sedation and unsteadiness was observed to increase with age (see section 4.8).
Age does not appear to have a significant effect on lorazepam kinetics (see section 5.2)

Clinical circumstances, some of which may be more common in the elderly, such as hepatic or renal impairment, should be considered. Greater sensitivity (e.g., sedation) of some older individuals cannot be ruled out. In general, dose selection for an elderly patient should be cautious, and lower doses may be sufficient in these patients (see section 4.2).
Elderly patients should be warned of the risk of falls due to the myorelaxant effect of lorazepam

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

Essential Laboratory Tests
Some patients on lorazepam have developed leukopenia, and some have had elevations of LDH.
As with other benzodiazepines, periodic blood counts and liver-function tests are recommended for patients on long-term therapy.

4.5 Interaction with other medicinal products and other forms of interaction

Not recommended:

Concomitant intake with alcohol

The sedative effects may be enhanced when the product is used in combination with alcohol. This affects the ability to drive or use machines.

Sodium oxybate
Avoid concomitant use (enhanced effects of sodium oxybate)

HIV-protease inhibitors
Avoid concomitant use (increased risk of prolonged sedation – see below for zidovudine)

Take into account

Centrally acting drugs

The benzodiazepines, including lorazepam, produce additive CNS depressant effects, including respiratory depression when co-administered with other medications which themselves produce CNS depression e.g., opioids, barbiturates, antipsychotics, sedative/hypnotics, anxiolytics, antidepressants, neuroleptics, narcotic analgesics, sedative antihistamines, anticonvulsants, and anesthetics. The elderly may require special supervision.

Anti-epileptic drugs
Pharmacokinetic studies on potential interactions between benzodiazepines and antiepileptic drugs have produced conflicting results. Both depression and elevation of drug levels, as well as no change have been reported.
Concurrent administration of lorazepam with sodium valproate may result in increased plasma concentrations and reduced clearance of lorazepam. Lorazepam dosage should be reduced to approximately 50% when coadministered with sodium valproate.
Valproate may inhibit the glucuronidation of lorazepam (increased serum levels: increased risk of drowsiness).
Phenobarbital taken concomitantly may result in an additive CNS effect. Special care should be taken in adjusting the dose in the initial stages of treatment.
Side effects may be more evident with hydantoins or barbiturates.

Narcotic analgesics
An enhancement of the euphoria induced by narcotic analgesics may occur with benzodiazepine use, leading to an increase in psychic dependence.

Clozapine
There have been reports of marked sedation, excessive salivation, hypotension ,delirium, respiratory arrest and ataxia when lorazepam and clozapine have been given concomitantly.

Other drugs enhancing the sedative effect of diazepam
Cisapride, lofexidine, nabilone, disulfiram and the muscle relaxants – baclofen and tizanidine

There have been reports of excessive stupor, significant reduction in respiratory rate and, in one patient, hypotension when lorazepam and loxapine have been given concomitantly.

Compounds that affect hepatic enzymes (particularly cyctochrome P450)
• Inhibitors (e.g. cimetidine, isoniazid; erythyromycin; omeprazole; esomeprazole) reduce clearance and may potentiate the action of benzodiazepines. Itraconazole, ketoconazole and to a lesser extent fluconazole and voriconazole are potent inhibitors of the cytochrome P450 isoenzyme CYP3A4 and may increase plasma levels of benzodiazapines. The effects of benzodiazapines may be increased and prolonged by concomitant use. A dose reduction of the benzodiazepine may be required.

• Inducers (e.g. rifampicin) may increase clearance of benzodiazepines

Antihypertensives, vasodilators and diuretics: Enhanced hypotensive effect with ACE-inhibitors, alpha-blockers, angiotensin-II receptor antagonists, calcium channel blockers, adrenergic neurone blockers, beta-blockers, moxonidine, nitrates, hydralazine, minoxidil, sodium nitroprusside and diuretics.

Enhanced sedative effect with alpha-blockers or moxonidine.

Dopaminergics
Possible antagonism of the effect of levodopa

Antacids
Concurrent use may delay absorption of lorazepam

Zidovudine
Increased zidovudine clearance by lorazepam

Oestrogen-containing contraceptives
Possible inhibition of hepatic metabolism of lorazepam

Theophylline/aminophylline
Administration of theophylline or aminophylline increase metabolism of lorazepam which may reduce the sedative effects of benzodiazepines, including lorazepam.

probenecid
Concurrent administration of lorazepam with probenecid may result in a more rapid onset or prolonged effect of lorazepam due to increased half-life and decreased total clearance. Lorazepam dosage needs to be reduced by approximately 50% when coadministered with probenecid.
The effects of probenecid and valproate on lorazepam may be due to inhibition of glucuronidation.

Caffeine
Concurrent use may result in reduced sedative and anxiolytic effects of lorazepam.

Grapefruit juice
Inhibition of CYP3A4 may increase the plasma concentration of lorazepam (possible increased sedation and amnesia).This interaction mat be of little significance in healthy individuals, but it is clear is if other factors such as old age or liver cirrhosis increase the risk of adverse events with concurrent use.

4.6 Fertility, pregnancy and lactation

Reproductive studies in animals were performed in mice, rats, and two strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull, and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all of these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At doses of 40 mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses.
The clinical significance of the above findings is not known**.**

Benzodiazepines should not be used during pregnancy, especially during the first and last trimesters. Benzodiazepines may cause fetal damage when administered to pregnant women. In particular, an increased risk of congenital malformations associated with the use of benzodiazepines during the first trimester of pregnancy has been suggested in several studies. In humans, umbilical cord blood samples indicate placental transfer of benzodiazepines and their glucuronide metabolites.

If the drug is prescribed to a woman of childbearing potential, she should be warned to contact her physician about stopping the drug if she intends to become, or suspects that she is, pregnant.

If, for compelling medical reasons, the product is administered during the late phase of pregnancy, or during labour at high doses, effects on the neonate can be expected due to the pharmacological action of the compound.

There is a possibility that infants born to mothers who take benzodiazepines chronically during the later stages of pregnancy may develop physical dependence. Infants of mothers who ingested benzodiazepines for several weeks or more preceding delivery have been reported to have withdrawal symptoms during the postnatal period. Symptoms such as, hypoactivity, hypotonia, hypothermia, respiratory depression, apnoea, feeding problems, and impaired metabolic response to cold stress have been reported in neonates born of mothers who have received benzodiazepines during the late phase of pregnancy or at delivery.

There is evidence that Lorazepam is excreted, albeit in pharmacologically insignificant amounts, in human breast milk. Therefore, Lorivan should not be given to breastfeeding mothers unless the expected benefit to the mother outweighs the potential risk to the infant. Sedation and inability to suckle

have occurred in neonates of lactating mothers taking benzodiazepines. Infants of lactating mothers should be observed for pharmacological effects (including sedation and irritability).

4.7 Effects on ability to drive and use machines

Patients should be advised that sedation, amnesia, dizziness, blurred vision, impaired concentration and impaired muscular function may occur and that, if affected, they should not drive or to use machines, or take part in other activities where this would put themselves or others at risk. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased (see also interactions). Concurrent medication may increase these effects (see section 4.5).

4.8 Undesirable effects

Adverse reactions, when they occur, are usually observed at the beginning of therapy and generally decrease in severity or disappear with continued use or upon decreasing the dose.

Most frequently reported adverse reactions associated with benzodiazepines include daytime drowsiness, dizziness, muscle weakness, and ataxia.
Adverse reactions are listed in the following table in CIOMS frequency categories:

Very common	≥10%
Common	≥1%
Uncommon	≥0.1% and <1%
Rare	≥0.01% and <0.1%
Very rare	<0.01%

General disorders:	
Frequency undetermined:	autonomic manifestations
Common: *Very rare:*	Asthenia hypothermia
Immune system disorders	
Frequency undetermined: *Very rare:*	*angioedema* Hypersensitivity including anaphylaxis/anaphylactoid reactions
Musculoskeletal disorders	
Common:	muscle weakness
Reproductive system and breast disorders	
Uncommon:	impotence
Cardiovascular:	
Frequency undetermined: *Rare:*	lowering in blood pressure hypotension (see section 4.4)
Digestive:	

Uncommon: *Rare:*	nausea constipation, salivation changes
Hepatobiliary disorders:	
Rare:	abnormal liver function test values (increase in bilirubin, transaminases, alkaline phosphatase), jaundice
Haematological/lymphatic:	
Very rare:	thrombocytopenia, agranulocytosis, pancytopenia, leucopenia
Nervous system:	
Frequency undetermined:	Benzodiazepine effects on the CNS are dose dependent, with more severe CNS depression occurring with high doses. Vertigo, convulsions/seizures, balance disorder, disorientation
Very common:	sedation, fatigue, drowsiness
Common:	Ataxia, dizziness, unsteadiness
Rare: *Very rare:*	headache, reduced alertness, dysarthria/slurred speech, transient anterograde amnesia or memory impairment. tremor, extrapyramidal symptoms, coma (see 4.9 Overdose)
Psychiatric disorders	
Frequency undetermined: *Common:* *Uncommon:* *Rare*	Dependence, suicidal ideation/attempt, impaired attention/concentration Paradoxical reactions including anxiety, agitation, excitation, hostility, aggression, rage, sexual arousal, hallucinations confusion, depression, unmasking of depression change in libido, decreased orgasm numbed emotions, appetite changes, sleep disturbances/insomnia, disinhibition, euphoria
Eye disorders	
Rare:	eye-function/visual disturbances (including diplopia and blurred vision)
Respiratory thoracic and mediastinal disorders:	
Rare:	Respiratory depression, apnoea, worsening of sleep apnoea (the extent of respiratory depression with benzodiazepines is dose dependent, with more severe

	depression occurring with high doses), worsening of obstructive pulmonary disease (see 4.9 Overdose).
Skin and subcutaneous tissue disorders:	
Frequency undetermined:	allergic skin reactions, alopecia, dermatological symptoms
Rare:	rash, allergic dermatitis
Endocrine disorders	
Very rare:	Inappropriate antidiuretic hormone secretion, hyponatraemia

Pre-existing depression may emerge during benzodiazepine use.

The incidence of sedation and unsteadiness increased with age.

Transient anterograde amnesia or memory impairment may occur using therapeutic doses, the risk increasing at higher doses (see section 4.4)

Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, delusion, rage, nightmares, hallucinations, psychoses, and inappropriate behaviour have been occasionally reported during benzodiazepine use. Such reactions may be more likely to occur in children and the elderly (see section 4.4).

Use (even at therapeutic doses) may lead to physical or psychological dependence and discontinuation of treatment may result in withdrawal reactions or rebound phenomena (see section 4.4).

Drug withdrawal symptoms (see section 4.4)

4.9 Overdose

In the management of overdosage with any drug, it should be borne in mind that multiple agents may have been taken. In postmarketing experience, overdose with lorazepam has occurred predominantly in combination with alcohol and/or other drugs.

Overdosage 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, and especially when other CNS-depressant drugs or alcohol are ingested, symptoms may include dysarthria, hypnotic state, ataxia, paradoxical reactions, CNS depression, hypotension, hypotonia, respiratory depression, cardiovascular depression, coma, and very rarely, death.

When there is a risk of aspiration, induction of emesis is not recommended. If ingestion was recent, induced vomiting and/or gastric lavage should be undertaken followed by general supportive care, monitoring of vital signs and close observation of the patient. Gastric lavage may be indicated in symptomatic patients**.** If there is no advantage in emptying the stomach, activated charcoal may be effective in reducing drug absorption. Hypotension, though unlikely usually may be controlled with noradrenaline. Lorazepam is poorly dialysable. Lorazepam glucuronide, the inactive metabolite, may be highly dialysable.

The benzodiazepine antagonist, flumazenil may be useful in hospitalised patients as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Flumazenil product information should be consulted prior to use. The physician should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological class: Benzodiazepine

Therapeutic class: Anxiolytic

ATC code: NO5BA06

Lorazepam is a benzodiazepine with anxiolytic, sedative, hypnotic and muscle relaxant properties.

5.2 Pharmacokinetic properties

Lorazepam is almost completely absorbed from the gastrointestinal tract and peak serum levels are reached in 2 hours, peak plasma level of lorazepam from a 2 mg dose is approximately 20 ng/mL. It is metabolised by a simple one-step process to a pharmacologically inert glucuronide. There are no major active metabolites. The elimination half-life is about 12 hours and there is minimal risk of excessive accumulation. At clinically relevant concentrations, lorazepam is approximately 90% bound to plasma proteins.The plasma levels of lorazepam are proportional to the dose given.

Studies comparing young and elderly subjects have shown that advancing age does not have a significant effect on the pharmacokinetics of lorazepam. However, in one study involving single intravenous doses of 1.5 to 3 mg of lorazepam Injection, mean total body clearance of lorazepam decreased by 20% in 15 elderly subjects of 60 to 84 years of age compared to that in 15 younger subjects of 19 to 38 years of age.

5.3 Preclinical safety data

Oesophageal dilation occurred in rats treated with lorazepam for more than one year at 6 mg/kg/day.

Carcinogenesis and mutagenesis

No evidence of carcinogenic potential emerged in rats during an 18-month study with lorazepam.
No studies regarding mutagenesis have been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipient(s)

Lactose monohydrate

Sodium starch glycollate

Cellulose microcrystalline

Magnesium stearate.

Carmellose sodium

6.2 Incompatibilities

Not Applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

PVC- White aluminium blisters packs of 20, 50 and 1,000 tablets**.**
Not all pack sizes maybe marketed

6.6 Special precautions for disposal and other handling

No special requirements

7. LICENSE HOLDER

Dexcel Ltd., 1 Dexcel Street, Or Akiva 3060000, Israel

8. MANUFACTURER
Dexcel Ltd., 1 Dexcel Street, Or Akiva 3060000, Israel

The format of this leaflet was determined by the Ministry of Health (MOH) and its content was checked and approved by the MOH in 06/2015.