Patient Information Leaflet (PIL)

Trabilin™ - 100 mg, solution for injection

Tramadol hydrochloride

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet

1. SERIOUS SIDE EFFECTS

WARNING: RISK FROM CONCOMITANT USE WITH OPIOIDS

Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death [see "Take special care with Trabilin", "Taking other medicines, herbal or dietary supplements"].

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

2. WHAT TRABILIN IS AND WHAT IT IS USED FOR?

The active substance in Trabilin is tramadol hydrochloride.
Moderate to severe, acute or prolonged pain and/or in cases where the effect of non-opioid analgesics is insufficient.

3. BEFORE YOU TAKE TRABILIN

a. Do not use Trabilin

- in cases of hypersensitivity to tramadol or to any of the excipients.
- in cases of acute intoxication with alcohol, hypnotics, analgesics, opioid or psychotropic agents.
- in patients receiving selective or non-selective MAO (monoamine oxidase) inhibitors (including selegiline) or who have used them within the last 14 days (see "Before you take Trabilin" section under "Taking other medicines, herbal or dietary supplements").
- in patients whose epilepsy cannot be sufficiently controlled by treatment.

- as a drug substitute. Although tramadol is an opioid agonist, it cannot suppress morphine withdrawal symptoms.
- in children younger than 12 years of age.
- in postoperative management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy.

b. Take special care with Trabilin

Trabilin must be used with particular caution in patients with opioid dependence, head injury, shock, disturbances of consciousness of uncertain origin, respiratory centre and respiratory function disorders, or conditions with increased intracranial pressure.

Seizures have been reported in patients taking the recommended dose of tramadol. There may be an increased risk if the recommended daily dose (400 mg) is exceeded. This risk also exists with concomitant ingestion of medicinal products which lower the seizure threshold or which may have adrenergic effects on the CNS, such as tricyclic antidepressants, antipsychotic agents, MAO inhibitors and serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs). Patients who have epilepsy or are susceptible to seizures should be treated with tramadol only in compelling exceptional cases (see "Possible side effects" section under "Nervous system disorders").

Trabilin is not intended for use in children below one year of age.

Tramadol has mild dependence potential. Tolerance, as well as psychological and physical dependence, may occur during prolonged use.

Thus, in patients who are prone to medication abuse or dependence, treatment with Trabilin must be restricted to short-term use under strict medical supervision (see also "Possible side effects" section). The medicinal product should be used with caution in patients who are sensitive to opioids. Trabilin is not suitable as substitution treatment in opioid dependence. Although tramadol is an opioid agonist, it cannot suppress morphine withdrawal symptoms (see "Before you take Trabilin" section under "Do not use Trabilin").

Relapses have been observed on Trabilin in patients with a history of opioid dependence.

Withdrawal symptoms may occur on abrupt cessation of Trabilin (see also "Possible side effects" section). Clinical experience suggests that withdrawal symptoms can be alleviated by tapering off the dose. With intravenous administration, Trabilin must be injected slowly.

Risks from Concomitant Use with Opioids

Concomitant use of benzodiazepines, including Trabilin and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of benzodiazepines and opioids 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 Trabilin 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. Advise both patients and caregivers about the risks of respiratory depression and sedation when Trabilin is used with opioids (see "Taking other medicines, herbal or dietary supplements").

c. Taking other medicines, herbal or dietary supplements

Trabilin must not be combined with selective or non-selective MAO inhibitors (including selegiline) (see "Before you take Trabilin" section under "Do not use Trabilin"). In the case of premedication with MAO inhibitors within the last 14 days prior to administration of the opioid pethidine, life-threatening interactions affecting the central nervous system and

cardiorespiratory function have been observed. The same interactions with MAO inhibitors cannot be excluded with Trabilin.
A reciprocal potentiation of the central effects should be expected on co-administration of Trabilin with other CNS depressants, including alcohol.
Prolongation of anaesthesia was observed in animal studies when Trabilin was combined with, for example, barbiturates. At the same time, however, a favourable effect on the perception of pain can be expected when Trabilin is combined with a tranquilliser, for example.
Based on the pharmacokinetic data available, no clinically relevant interactions should be expected with concomitant or prior administration of cimetidine (an enzyme inducer).
Concomitant or prior administration of carbamazepine (an enzyme inhibitor) may lead to a reduced analgesic effect and a shorter duration of action.
Tramadol may trigger seizures and increase the seizure-inducing potential of selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants, antipsychotics and other seizure threshold-lowering agents (such as bupropion, mirtazapine and tetrahydrocannabinol).
Concomitant therapy with tramadol and serotonergic medicinal products such as SSRIs, SNRIs or MAO inhibitors, tricyclic antidepressants and mirtazapine can cause serotonin syndrome.
Signs of serotonin syndrome may be:

- Spontaneous clonus
- Inducible or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Muscular hypertension and body temperature above 38 °C and inducible or ocular clonus.

In such cases, discontinuation of medicinal products with serotonergic properties generally brings about a rapid improvement. Pharmacotherapy depends on the nature and severity of the symptoms that occur.
If tramadol and coumarin derivatives (e.g. warfarin) are coadministered, the patient must be carefully monitored, as increased INR (International Normalised Ratio) values with major haemorrhages and ecchymoses have been observed in some patients.
CYP3A4 inhibitors, such as ketoconazole and erythromycin, can inhibit the metabolism of both tramadol (N-demethylation) and possibly the active O-demethylated metabolite. The clinical significance of this interaction is not known (see also “Possible side effects” section).
Studies of *in vitro* interactions using human liver microsomes indicate that co-administration with CYP2D6 inhibitors such as fluoxetine, paroxetine and amitriptyline may lead to some inhibition of tramadol metabolism.
In a limited number of studies, pre- and postoperative administration of ondansetron, an antiemetic 5-HT_3 antagonist, increased the need for tramadol in patients with postoperative pain.
Ultra-Rapid Metabolism of Tramadol and Other Risk Factors for Life-threatening Respiratory Depression in Children
Life-threatening respiratory depression and death have occurred in children who received tramadol. Tramadol and codeine are subject to variability in metabolism based upon CYP2D6 genotype (described below), which can lead to increased exposure to an active metabolite.
Based upon post marketing reports with tramadol or with codeine, children younger than 12 years of age may be more susceptible to the respiratory depressant effects of tramadol.
Furthermore, children with obstructive sleep apnea who are treated with opioids for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to their respiratory depressant effect. Because of the risk of life-threatening respiratory depression and death: Trabilin is contraindicated for all children younger than 12 years of age.

Trabilin is contraindicated for post-operative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy.
Avoid the use of Trabilin in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol unless the benefits outweigh the risks. Risk factors include conditions associated with hypoventilation, such as postoperative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression.
As with adults, when prescribing opioids for adolescents, healthcare providers should choose the lowest effective dose for the shortest period of time and inform patients and caregivers about these risks and the signs of opioid overdose.
Nursing Mothers
Tramadol is subject to the same polymorphic metabolism as codeine, with ultra-rapid metabolizers of CYP2D6 substrates being potentially exposed to life-threatening levels of O-desmethyltramadol (M1). At least one death was reported in a nursing infant who was exposed to high levels of morphine in breast milk because the mother was an ultra-rapid metabolizer of codeine. A baby nursing from an ultra-rapid metabolizer mother taking Trabilin could potentially be exposed to high levels of M1, and experience life-threatening respiratory depression. For this reason, breastfeeding is not recommended during treatment with Trabilin.
CYP2D6 Genetic Variability: Ultra-rapid metabolizer Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype (gene duplications denoted as *1/*1xN or *1/*2xN). The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 1 to 10% for Whites (European, North American), 3 to 4% for Blacks (African Americans), 1 to 2% for East Asians (Chinese, Japanese, Korean), and may be greater than 10% in certain racial/ethnic groups (i.e., Oceanian, Northern African, Middle Eastern, Ashkenazi Jews, Puerto Rican).
These individuals convert tramadol into its active metabolite, Odesmethyltramadol (M1), more rapidly and completely than other people do. This rapid conversion results in higher than expected serum M1 levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing). Therefore, individuals who are ultra-rapid metabolizers should not use Trabilin.

The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the brain (central nervous system) that control respiration. Benzodiazepines interact at $GABA_A$ 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

d. Pregnancy and breast-feeding
Pregnancy
Tramadol crosses the placenta. There are no adequate data on the safety of tramadol in human pregnancy. In animal studies, effects on reproductive toxicity, but no teratogenic effects, occurred at very high maternally toxic doses.
Tramadol has no effect on uterine contractility before or during delivery. In the neonate, it may cause changes in the respiratory rate which are generally of no clinical significance.
Long-term use of tramadol during pregnancy can lead to withdrawal symptoms in the neonate.

Trabilin should not be administered to pregnant women unless it is clearly necessary.
Breastfeeding
During lactation, tramadol is excreted in breast milk in a proportion approximately equivalent to 0.1% of maternal plasma concentrations. Trabilin should not be administered to breastfeeding women or used by breastfeeding women. Discontinuation of breastfeeding is not normally required following single-dose administration.
Fertility
In post-marketing surveillance, a few cases of sperm abnormalities and hypogonadism have been reported. However, no causal relationship could be established. Animal studies have shown no effect of tramadol on fertility.

e. Driving and using machines
Even when used as directed, Trabilin may alter the reactions (e.g. induce drowsiness and dizziness) to such an extent that the ability to drive or use machines is impaired. This particularly applies in combination with alcohol or other psychotropic agents.

4. HOW TO TAKE TRABILIN
Dosage should be adjusted to the severity of pain and individual patient sensitivity. In general, the lowest analgesically effective dose should be selected. A daily total dose of 400 mg tramadol hydrochloride must not be exceeded, except in special circumstances.
Solution for injection 100 mg/2 ml
Adults and children over 12 years of age
50–100 mg tramadol hydrochloride every 4–6 hours
Children over 1 year of age
Single dose of 1-2 mg/kg body weight; maximum daily doses of 8 mg tramadol hydrochloride per kg body weight or 400 mg tramadol hydrochloride, whichever is lower, must not be exceeded.
Use of the solution for injection/dilution
Instructions for handling
Trabilin 100 mg/2 ml solution for injection
How to calculate the volume to be injected
1) Calculate the total dose of tramadol hydrochloride (mg) required as follows: body weight (kg) × dose (mg/kg).
2) To calculate the volume (ml) of diluted solution to be injected, divide the total dose (mg) by an appropriate concentration of the diluted solution (mg/ml; see table).
Table: Dilution of Trabilin solution for injection

Trabilin 100 mg/2 ml + diluent to be added	Concentration of diluted solution for injection (mg tramadol hydrochloride/ml)
2 ml + 2 ml	25.0 mg/ml
2 ml + 4 ml	16.7 mg/ml
2 ml + 6 ml	12.5 mg/ml
2 ml + 8 ml	10.0 mg/ml
2 ml + 10 ml	8.3 mg/ml
2 ml + 12 ml	7.1 mg/ml
2 ml + 14 ml	6.3 mg/ml

2 ml + 16 ml	5.6 mg/ml
2 ml + 18 ml	5.0 mg/ml

Based on the calculated volume, dilute one tramadol ampoule by adding a suitable diluent and mix. The calculated dilution volume can be used without taking account of the volume extension.

Patients with renal or hepatic disorders

In patients with renal and/or hepatic insufficiency, elimination of tramadol is delayed; the duration of action of Trabilin may therefore be prolonged. If appropriate, the dosage interval should be extended, depending on the recurrence of painful conditions.

Patients requiring dialysis

Due to its large volume of distribution, tramadol is only very slowly eliminated from the serum by haemodialysis or haemofiltration. Post-dialysis administration to maintain analgesia is therefore not usually necessary in patients requiring dialysis.

Elderly patients

In general, no dose adjustment is required for patients up to 75 years of age without clinically manifest hepatic or renal dysfunction. Elimination may be prolonged in patients over 75 years, even those without clinically manifest hepatic or renal dysfunction. Consequently, dosing intervals must, if necessary, be extended depending on patient need.

Duration of therapy

Trabilin should not be used for longer than therapeutically absolutely necessary. If, depending on the nature and severity of the disorder, prolonged pain management with Trabilin seems necessary, careful reviews should be carried out regularly at short intervals (if necessary with breaks in treatment), in order to establish whether and to what extent such treatment is still medically required.

5. POSSIBLE SIDE EFFECTS

The most common side effects are nausea and dizziness, both occurring in more than 10% of patients.

Nervous system disorders

Very common (>10%): dizziness (14%).

Common (1-10%): headache, drowsiness.

Rare (0.01-0.1%): speech disorders, paraesthesia, tremor, seizures, involuntary muscle twitching, coordination disorders, syncope.

Seizures have mainly occurred after use of high doses of tramadol or following concomitant use of medicinal products with potential for lowering the seizure threshold (see "Before you take Trabilin" section under "Take special care with Trabilin" and "Taking other medicines, herbal or dietary supplements").

Psychiatric disorders

Rare (0.01-0.1%): hallucinations, confusional state, sleep disorders, delirium, anxiety and nightmares.

Various psychiatric side effects, which vary individually in intensity and nature (depending on personality and duration of treatment), may occur following administration of Trabilin. These include mood changes (usually elation, occasionally dysphoria), changes in activity (usually suppression, occasionally increase) and changes in cognitive and sensory performance (e.g. decision-making behaviour, perception disorders).

Dependence may occur.

Symptoms of withdrawal syndromes, similar to those occurring during opioid withdrawal, may occur. Such symptoms are: agitation, anxiety, nervousness, sleep disorders, hyperkinesia, tremor and gastrointestinal symptoms.

Other very rare symptoms (<0.01%) observed upon discontinuation of tramadol include: panic attacks, severe anxiety, hallucinations, paraesthesia, tinnitus and unusual CNS symptoms (e.g. confusion, delusions, depersonalisation, derealisation, paranoia).
Eye disorders
Rare (0.01-0.1%): miosis, mydriasis, blurred vision.
Cardiac disorders
Uncommon (0.1-1%): effects on circulatory regulation (palpitations, tachycardia). These undesirable effects may particularly occur after intravenous administration and in patients under physical stress.
Rare (0.01-0.1%): bradycardia
Investigations
Rare (0.01-0.1%): increased blood pressure
Vascular disorders
Uncommon (0.1-1%): effects on circulatory regulation (orthostatic hypotension or circulatory collapse). These undesirable effects may particularly occur after intravenous administration and in patients under physical stress.
Metabolism and nutrition disorders
Rare (0.01-0.1%): changes in appetite.
Frequency not known: hypoglycaemia
Respiratory, thoracic and mediastinal disorders
Rare (0.01-0.1%): respiratory depression, dyspnoea.
Respiratory depression may occur if the recommended dosage is considerably exceeded and with concomitant use of other CNS depressants.
Exacerbation of asthma has been reported. However, no causal relationship could be established.
Gastrointestinal disorders
Very common (>10%): nausea (15%).
Common (1-10%): vomiting (9%), constipation, dry mouth.
Uncommon (0.1-1%): retching, gastrointestinal discomfort (e.g. stomach pressure, fullness), diarrhoea.
Hepatobiliary disorders
In very rare cases, elevated liver enzymes have been reported in temporal association with the therapeutic use of tramadol.
Skin and subcutaneous tissue disorders
Common (1-10%): hyperhidrosis
Uncommon (0.1-1%): cutaneous reactions (e.g. pruritus, erythema, urticaria)
Musculoskeletal and connective tissue disorders
Rare (0.01-0.1%): motor weakness
Renal and urinary disorders
Rare (0.01-0.1%): micturition disorders (dysuria and urinary retention).
Immune system disorders
Rare (0.01-0.1%): allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angio-oedema) and anaphylaxis.
General disorders and administration site conditions
Common (1-10%): exhaustion.
Overdose
Symptoms
In principle, the same symptoms as those for other opioids can be expected to occur in cases of intoxication with Trabilin. In particular, the following are possible: miosis, vomiting, circulatory collapse, drowsiness or even loss of consciousness, coma, seizures and respiratory depression to the point of respiratory paralysis.

Treatment
General emergency procedures for maintaining airway patency (aspiration) are applicable. Respiratory and cardiovascular function must be maintained depending on the symptoms. Naloxone can be used as an antidote for respiratory depression. In animal studies, naloxone was ineffective for treatment of seizures; in such cases, diazepam IV should be used. Opioid/benzodiazepine interaction must be considered (risk of respiratory depression).
Following intoxication with oral tramadol products, detoxification with activated charcoal or gastric lavage is recommended only within 2 hours of ingestion. Thereafter, such treatments are useful only if extremely large quantities or prolonged-release tablets have been ingested.
Tramadol is dialysable only to a small extent. For this reason, haemodialysis or haemofiltration alone is not suitable for the management of acute Trabilin intoxication.

6. HOW TO STORE TRABILIN

Do not store above 25 °C.
Once an ampoule of Trabilin 100 mg solution for injection has been opened, any solution remaining after use should be discarded.
The expiry date (EXP) printed on the pack should not be exceeded.

7. FURTHER INFORMATION

a. What Trabilin contains

Solution for injection: 100 mg tramadol hydrochloride / 2 ml, (IV/IM/SC).

b. What Trabilin looks like and contents of the pack

Trabilin 100, solution for injection: 5 ampoules of 2 ml [A]

c. Marketing Authorisation Holder and Manufacturer

Acino Pharma AG, Liesberg (Switzerland)

d. This leaflet was last approved in

June 2018

e. To report any side effects:

- ***Saudi Arabia:***

The National Pharmacovigilance and Drug Safety Centre (NPC)
Fax: +966-11-205-7662
Call NPC at +966-11-2038222, Exts: 2317-2356-2353-2354-2334-2340.
Toll free phone: 8002490000
E-mail: npc.drug@sfda.gov.sa
Website: www.sfda.gov.sa/npc

- ***Other GCC States:***

- Please contact the relevant competent authority.

f. Council of Arab Health Ministers

This is a
Medicament

- Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are the experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of reach of children.

Council of Arab Health Ministers
Union of Arab Pharmacists

g. This patient information leaflet is approved by the Saudi Food and Drug Authority