WARNING: RISK FROM CONCOMITANT USE WITH OPIOIDS
Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death [see Special warnings and precautions for use (4.4), Interaction with other medicinal products and other forms of interaction (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

1. NAME OF THE MEDICINAL PRODUCT

Trabilin™ - 100 mg, solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: tramadol hydrochloride.

Excipients:

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Moderate to severe, acute or prolonged pain and/or in cases where the effect of non-opioid analgesics is insufficient.

4.2 Posology and method of administration

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.
See the section "Undesirable effects", Children and adolescents.

Method of administration

The solution for injection should be administered slowly, i.e. 1 ml Tramadol solution for injection (equivalent to 50 mg tramadol hydrochloride) per minute, or should be diluted in a solution for infusion and infused.
For information on dilution of this medicinal product before use, see the section "Pharmaceutical Particulars", Instructions for handling.

Patients with renal or hepatic disorders

In patients with renal and/or hepatic insufficiency, elimination of tramadol is delayed; the duration of action of Tramadol 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

Tramadol should not be used for longer than therapeutically absolutely necessary. If, depending on the nature and severity of the disorder, prolonged pain management with Tramadol 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.

4.3 Contraindications

Tramadol is contraindicated:

- 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 "Interaction with other medicinal products and other forms of interaction" section).

- 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.
- children younger than 12 years of age.
- postoperative management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy.

4.4 Special warnings and precautions for use

Tramadol must be used with particular caution in patients with opioid dependence, head injury, shock, disturbances of consciousness of uncertain origin, respiratory centre or 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 "Undesirable effects" section under Nervous system disorders).

Tramadol 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 Tramadol must be restricted to short-term use under strict medical supervision (see also "Undesirable effects" section). The medicinal product should be used with caution in patients who are sensitive to opioids. Tramadol is not suitable as substitution treatment in opioid dependence. Although tramadol is an opioid agonist, it cannot suppress morphine withdrawal symptoms (see "Contraindications" section).

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

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

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, O-desmethyltramadol (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.

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 Interaction with other medicinal products and other forms of interaction 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Tramadol must not be combined with selective or non-selective MAO inhibitors (including selegiline) (see also “Contraindications” section). 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 Tramadol.

A reciprocal potentiation of the central effects should be expected on co-administration of Tramadol with other CNS depressants, including alcohol.

Prolongation of anaesthesia was observed in animal studies when Tramadol was combined with, for example, barbiturates. At the same time, however, a favourable effect on the perception of pain can be expected when Tramadol 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 inhibitor).
Concomitant or prior administration of carbamazepine (an enzyme inducer) 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 (see also "Contraindications" section), 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 co-administered, 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 "Undesirable 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.

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 $GABA_A$ 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.

4.6 Fertility, Pregnancy and lactation

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 (see "Preclinical data" section).

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.

Tramadol 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. Tramadol 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.

4.7 Effects on ability to drive and use machines

Even when used as directed, Tramadol 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.

4.8 Undesirable 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 "Special warnings and precautions for use" and "Interaction with other medicinal products and other forms of interaction" sections).

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 Tramadol. 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 (see "Interaction with other medicinal products and other forms of interaction" section).

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.

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.

4.9 Overdose

Symptoms

In principle, the same symptoms as those for other opioids can be expected to occur in cases of intoxication with Tramadol. 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 Tramadol intoxication.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: N02AX02

Tramadol is a centrally acting opioid analgesic. It is a non-selective pure agonist at μ, δ and κ opioid receptors with a greater affinity for the μ receptor. Other mechanisms which contribute to

an analgesic effect are inhibition of neuronal reuptake of noradrenaline and potentiation of serotonin release.

Tramadol possesses antitussive properties. Unlike morphine, tramadol has no respiratory depressant effect over a wide range of analgesic doses. Equally, gastrointestinal motility is affected to a lesser extent. Effects on the cardiovascular system tend to be minor. The analgesic potency of tramadol is reported to be 1/10 to 1/6 that of morphine.

Tramadol has a rapid onset of analgesic effect, which lasts for several hours (4-6 h).

Children and adolescents

The effects of enteral and parenteral tramadol administration were studied in clinical trials with more than 2,000 paediatric patients from newborns to 17-year-olds. The indications for pain treatment examined in these studies were pain following operations (especially abdominal), following surgical dental extractions, as a result of fractures, burns and trauma, as well as other painful conditions expected to require analgesic treatment for 7 days.

The efficacy of tramadol was superior to placebo and greater than or equal to that of paracetamol, nalbuphine, pethidine or low-dose morphine in single doses of up to 2 mg/kg or repeated dose of up to 8 mg/kg per day (up to a maximum of 400 mg per day). The studies conducted have confirmed the efficacy of tramadol. The safety profile of tramadol was similar in adults and paediatric patients over 1 year (see “Posology and method of administration” section).

5.2 Pharmacokinetic properties

Absorption

Over 90% of tramadol is absorbed following oral administration. The absolute bioavailability of orally administered tramadol, which is independent of concomitant food intake, is about 68% and that of rectally administered tramadol about 79%. Compared to other analgesics, this is within an extremely favourable range. First-pass metabolism is not more than 30% after oral administration and not more than 20% after rectal administration.

The half-life of the distribution phase $t_{1/2\alpha}$ is approximately 0.8 h. After administration of 100 mg in liquid or solid form, the peak plasma concentration C_{max} is 309 ± 90 ng/ml or 280 ± 49 ng/ml, respectively, and is reached after 1.2 h or 2 h, respectively. Following IV injection of 100 mg, peak plasma levels of 613 ± 221 ng/ml are measured after 15 minutes.

There is a correlation between serum concentration and analgesic action, but with wide intraindividual variations. A serum concentration of 100-300 ng/ml is generally effective.

Distribution

Tramadol shows high tissue affinity. The volume of distribution is 203 ± 40 l. Serum protein binding is approximately 20%.

Tramadol crosses the blood-brain barrier and the placenta. Very small amounts of tramadol, together with its O-desmethyl derivative, are found in breast milk (0.1% and 0.02% of the administered dose, respectively).

Metabolism/Elimination

The elimination half-life $t_{1/2\beta}$ of tramadol is about 6 h, irrespective of the method of administration.

In humans, tramadol is mainly metabolised by N- and O-demethylation and by glucuroconjugation of the O-demethylated products. Only O-desmethyl-tramadol is pharmacologically active, but its concentration in blood is less than that of tramadol itself. According to animal studies, the potency of O-desmethyl-tramadol exceeds that of the parent compound by a factor of 2-4. Its elimination half-life $t_{1/2\beta}$ is 7.9 h and is of the same magnitude as that of tramadol.

Inhibition of the isoenzymes CYP3A4 and/or CYP2D6 involved in the biotransformation of tramadol may affect the plasma concentration of tramadol or its active metabolite. No clinically significant interactions have been reported to date.

Tramadol and its metabolites are almost exclusively eliminated via the kidneys (up to 90%). About a quarter to a third of the active substance is excreted unchanged in the urine.

Kinetics in special patient groups

No dose adjustment is necessary in acute pain, as Tramadol is administered only once or a few times. In the case of chronic pain, no dose adjustment is generally necessary for elderly patients (up to 75 years of age) without clinically manifest hepatic or renal insufficiency. Elimination may be prolonged in old patients (over 75 years of age). Dosing intervals should therefore be extended as necessary on an individual basis.

Hepatic or renal dysfunction should be expected to result in prolongation of the terminal half-life; however, this is only minor as long as either of these two excretory organs is largely intact. The elimination half-life for tramadol determined in patients with liver cirrhosis was about 13 hours; in extreme cases, 22 hours.

In patients with renal insufficiency (creatinine clearance <5 ml/min), the values were about 11 hours and in extreme cases about 20 hours.

Children and adolescents

The pharmacokinetics of tramadol and O-desmethyltramadol following a single oral dose and repeated-dose administration in patients from 1 year to 16 years was generally similar to that in

adults when the dosage was adjusted to body weight, but with higher inter-individual variability in children aged 8 years and under.
The pharmacokinetics of tramadol and O-desmethyltramadol has not been fully characterised in children under 1 year. Information from studies that included this age group indicate that the formation rate of O-desmethyltramadol via CYP2D6 in neonates rises continuously and reaches the CYP2D6 adult activity level at approximately 1 year of age. Moreover, an immature glucuronidation system and immature renal function lead to slower elimination and accumulation of O-desmethyltramadol in children under 1 year. For this reason, tramadol should not be used in this age group.

5.3 Preclinical safety data

Results from the tests performed showed no indications of a potential genotoxic risk for tramadol.
From a study in rats, there was no evidence of any substance-related increase in tumour incidences. In the study in mice, an increased incidence of liver cell adenomas in males was observed (from 15 mg/kg; a dose-dependent, non-significant increase), as well as an increase in lung tumours among females in all dose groups (a significant yet non-dose-dependent increase).
At very high, maternally toxic doses of tramadol hydrochloride (equivalent to 3 to 15 times the maximum human dose), studies in mice, rats and rabbits showed effects on organ development, ossification, as well as embryonic and foetal mortality. Fertility and the development of pups were not affected.
No impairment of male or female fertility in adult animals was observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate, nitrogen, water for injections sufficient for 2 ml of solution; 1 ml of solution for injection contains 0.7 mg sodium.

6.2 Incompatibilities

Tramadol solutions for injection have been shown to be incompatible (immiscible) with solutions for injection containing:

- diazepam
- diclofenac
- flunitrazepam

- glyceryl trinitrate
- indometacin
- midazolam
- phenylbutazone

6.3 Shelf life

36 months

Once an ampoule of Tramadol 100 mg solution for injection has been opened, any solution remaining after use should be discarded.

The medicinal product must not be used after the date which is stated on the packaging after "EXP".

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

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

6.6 Special precautions for disposal and other handling

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 Tramadol solution for injection

Tramadol 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.

7. MARKETING AUTHORISATION HOLDER

Acino Pharma AG, Liesberg (Switzerland)

8. MARKETING AUTHORISATION NUMBER

39-222-10

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first Authorization in Saudi Arabia

16/03/2010

10. DATE OF REVISION OF THE TEXT

June 2018