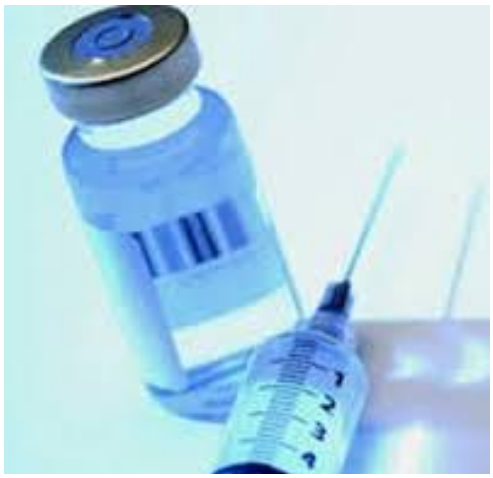
PRODUCT REGISTRATION DOSSIER

For

NIGERIA (NAFDAC)



FEXONA TRAMADOL INJECTION

(TRAMADOL HYDROCHLORIDE INJECTION 100mg/2ml)

MANUFACTURED BY:

Psychotropics India Limited

MODULE –I

Administrative Information

1.0 COVER LETTER

Enclosed

1.1 TABLE OF CONTENT

1.2 APPLICATION FORM

1.2.1 APPLICATION LETTER

1.2.2 Registration Form

1.2.3 Certificate of Incorporation

Enclosed

सत्यमेव जयते

Company No. 55-83911

FRESH CERTIFICATE OF INCORPORATION CONSEQUENT UPON CHANGE OF NAME ON CONVERSION TO PUBLIC LIMITED COMPANY

In the Office of the Registrar of Companies, N.C.T. of Delhi & Haryana
[under the Companies Act, 1956 (1 of 1956)]

IN THE MATTER OF M/s. PSYCHOTROPICS INDIA PRIVATE LIMITED

I hereby certify that PSYCHOTROPICS INDIA PRIVATE LIMITED which was originally incorporated on EIGHTH day of JULY Nineteen Hundred and Ninety EIGHTY under the Indian Companies Act, 1913 (Act VII of 1913)/Companies Act, 1956 (Act 1 of 1956) under the name PSYCHOTROPICS INDIA PRIVATE LIMTED having duly passed the necessary Special Resolution on 28.7.97 in terms of section 31/21 read with section 44 of the Companies Act, 1956, the name of the said Company is this day changed to PSYCHOTROPICS INDIA LIMITED and this Certificate is issued pursuant to Section 23(1) of the said Act.

Given under my hand at NEW DELHI this TWENTY FIFTH day of MARCH One Thousand Nine Hundred and Ninety EIGHT

रजिस्ट्रार ... राष्ट्रीय राजधानी क्षेत्र, दिल्ली एवं हरियाणा

Jha

(N.N. JHA)

ADDL. REGISTRAR OF COMPANIES,
N.C.T. OF DELHI AND HARYANA

1.2.4 Power of Attorney

Enclosed

1.2.5 Notarized Declaration of the Applicant

1.2.6 Power of Attorney/Contract manufacturing Agreement

1.2.7 Certificate of Pharmaceutical Product

1.2.8 Certificate of Good Manufacturing Product

Enclosed

OFFICE OF THE DRUGS CONTROLLING & LICENSING AUTHORITY
Directorate General of Medical Health & Family Welfare,
Sahastradhara Road, Dehradun (Uttarakhand)

File no. 17P/1/68/2010 8134 ***Date:*** 01 ***May. 2018***

Certificate of Good Manufacturing Practices

Certificate no.:17P/1/68/2010

On the basis of the Joint Inspection carried out on 05-04-2018 we certify that the site indicated on this certificate complies with Good Manufacturing Practices for the dosage forms, categories and activities listed in Table 1.

1. ***Name & Address of site:***
   M/s Psychotropics India Ltd.,
   Plot No- 12 & 12A, Industrial Park-2, Phase-I,
   Salempur,Mehdood-2, Haridwar, Uttarakhand
2. ***Manufacturer's license number:***
   Form 25- 28/UA/2010
   Form 28- 30/UA/SC/P-2010
   Form 28-B-38/UA/X/SC/P-2014
3. ***Table 1:***

Dosage form(s)	***Activity(ies)***
Tablets (Non Beta Lactum)	*Manufacturing & Testing*
Capsules Hard Gelatin (Non Beta Lectum)	*Manufacturing & Testing*
Liquid & Dry Powder Injection (Non Beta Lectum)	*Manufacturing & Testing*
Tablets (Cepha Block)	*Manufacturing & Testing*
Oral Suspension (Cepha Block)	*Manufacturing & Testing*
Dry Powder Injection (Cepha Block)	*Manufacturing & Testing*

The responsibility for the quality of the individual batches of the pharmaceutical products manufactured through this process lies with the manufacturer.

This certificate remains valid until 30-04-2020. It becomes invalid if the activities and/or categories certified herewith are changed or if the site is no longer considered to be in compliance with GMP.

The firm is following ***Good Manufacturing Practices as per World Health Organiazation(WHO)TRS Guide Lines,*** *in the Manufacturing & testing of the said categories of Products and Items in respect of which the Certificates of Pharmaceuticals products have been issued.*

Address of certifying Authority:
Directorate General of Medical Health & Family Welfare,
Sahastradhara Road, Dehradun (Uttarakhand) INDIA.
Name & function of responsible person:
Shri Tajber Singh
Drugs Licensing & Controlling Authority
Uttarakhand.
Email: *drugcontroluk@gmail.com*
Tel.no. *NA*
Fax. no. *0135260874*

11/5/18

(Tajber Singh)
Drugs Licensing & Controlling Authority
(Uttarakhand)

(Tajber Singh)
Drug Controlling & Licensing Authority (Mfg.)
Garhwal Mandal (Uttarakhand)

DRUGS LICENCING CUM CONTROLLING AUTHORITY * UTTARAKHAND * UTTARKHAND

sandeep/form

1.2.9 Manufacturing Authorization

1.2.10 Evidence of Trademark Registration

1.2.11 Superintendent Pharmacist's Annual License to practice

1.2.12 Certificate of Registration and retention of Premises

1.2.13 Evidence of Previous Marketing Authorisation

1.2.14 Invitation Letter of GMP Inspection

1.2.15 Copy of Certificate of suitability of the European Pharmacopoeia

1.2.16 Letter of Access of APIMF

1.2.17 Biowaiver Request in relation to conducting BCS-based bioavailability study

Not Applicable

1.2.18 Biowaiver Request in relation to conducting additional strength bioavailability

Not Applicable

1.3 Product Information

Enclosed

1.3.1 Summary of Pharmaceutical Characteristics

Enclosed

1.0 NAME OF MEDICINAL PRODUCT:

Fexona Tramadol Injection

2.0 QUALITATIVE AND QUANTITATIVE FORMULA:

QUALITATIVE AND QUANTITATIVE FORMULA	
Brand Name	FEXONA TRAMADOL INJECTION
Generic Name	Tramadol Hydrochloride Injection100mg/2ml
Label claim	Each 2ml contains: Tramadol Hydrochloride BP 100mg Water for Injections BP q.s

S.No.	Ingredients	Claim/ml	O.A.%	Spec.	Qty./ml	Percentage (%w/v)	Rational
Active:							
01	Tramadol Hydrochloride *	50 mg	**….**	BP	50.66mg	5.06%	Active
In-active:							
01	Disodium Edetate	**….**	**….**	BP	0.5mg	0.05%	Chelating Agent
02	Hydrochloric Acid	**….**	**….**	BP	0.0005ml	**….**	pH adjustment
03	Water for Injections	…..	**….**	BP	q.s to 1ml	**….**	Solvent
				Total	**51.16mg**	**…..**	

* Quantity of Active Raw Materials to be calculated on the basis of Calculation Sheet
Extractable Volume: The volume of each container is not less than nominal volume (2ml)
Abbreviations: **O.A.:** Overages Added, **Qty.:** Quantity, **Spec.:** Specification, **API:** Active Pharmaceutical Ingredients, **BP.:** British Pharmacopoeia.

3.0 PHARMACEUTICAL FORM:

Dosage Form **:** Solution for injection

4.0 CLINICAL PARTICULARS :

4.1 Therapeutic Indications :

For the treatment and prevention of moderate to severe pain.

Tramadol 50mg/ml Solution for Injection is a centrally acting analgesic. It is a non-selective pure agonist at mu, delta and kappa opioid receptors with a higher affinity for the mu receptor. Other mechanisms, which may contribute to its analgesic effect, are inhibition of neuronal reuptake of nor adrenaline and enhancement of serotonin release. Tramadol has an antitussive effect. In contrast to morphine, analgesic doses of tramadol over a wide range have no respiratory depressant effect. Also gastrointestinal motility is less affected. Effects on the cardiovascular system tend to be slight. The

potency of Tramadol is reported to be 1/10 (one tenth) to 1/6 (one sixth) that of morphine.

4.2 Posology and method of Administration :

Tramadol Hydrochloride Injection 100mg/2ml should not be administered for longer than absolutely necessary. If long-term pain treatment with Tramadol Hydrochloride Injection 100mg/2ml is necessary in view of the nature and severity of the illness, then careful regular monitoring should be carried out (if necessary with breaks in treatment) to establish whether, and to what extent, further treatment is necessary.

The dose should be adjusted to the intensity of the pain and the sensitivity of the individual patient. The lowest effective dose for analgesia should generally be selected. The total daily dose of 400mg tramadol hydrochloride should not be exceeded, except in special clinical circumstances.

The tramadol solution is for parenteral injection either intramuscularly, by slow intravenous injection or diluted in solution for administration by infusion or patient controlled analgesia.

Adults and children 12 years and over:

The usual dose is 50mg or 100mg 4 to 6 hourly by either intramuscular or intravenous routes. Intravenous injections must be given slowly over 2–3 minutes. The dose should be adjusted according to the severity of the pain and the response.

For post-operative pain, an initial bolus of 100mg is administered. During the 60 minutes following the initial bolus, further doses of 50mg may be given every 10-20 minutes, up to a total dose of 250mg including the initial bolus. Subsequent doses should be 50mg or 100mg 4- 6 hourly up to a total daily dose of 400mg.

Geriatric patients

A dose adjustment is not usually necessary in patients up to 75 years without clinically manifest hepatic or renal insufficiency. In elderly patients over 75 years elimination may be prolonged. Therefore, if necessary the dosage interval is to be extended according to the patient's requirements.

Renal insufficiency/dialysis and hepatic impairment

In patients with renal and/or hepatic insufficiency the elimination of tramadol is delayed. In these patients prolongation of the dosage intervals should be carefully considered according to the patient's requirements.

Children under 12 years: Not recommended.

Method of administration: Intravenous & intramuscular Injection

4.3 Contraindications:

Tramadol Hydrochloride Injection 100mg/2ml should not be given to patients who have previously demonstrated hypersensitivity towards Tramadol or any of the other ingredients. Tramadol Hydrochloride Injection 100mg/2ml should not be given to patients suffering from acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic drugs. In common with other opioid analgesics, Tramadol should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal. Tramadol Hydrochloride Injection 100mg/2ml is contraindicated in patients with epilepsy not adequately controlled by treatment. Tramadol must not be used in narcotic withdrawal treatment.

4.4 Special warnings and precautions for use:

Warnings

- At therapeutic doses, tramadol has the potential to cause withdrawal symptoms. Rarely, cases of dependence and abuse have been reported.
- At therapeutic doses withdrawal symptoms have been reported at a frequency of 1 in 8,000. Reports of dependence and abuse have been less frequent. Because of this potential the clinical need for continued analgesic treatment should be reviewed regularly.
- Tramadol has a low dependence potential. On long term use tolerance, psychic and physical dependence may develop. In patients with a tendency to drug abuse or dependence, treatment should be for short periods and under strict medical supervision.
- Tramadol Hydrochloride Injection 100mg/2ml is not a suitable substitute in opioid dependent patients. The product does not suppress morphine withdrawal symptoms although it is an opioid agonist.
- Tramadol Hydrochloride Injection 100mg/2ml may cause drowsiness and this effect may be potentiated by alcohol and other CNS depressants. Ambulant patients should be warned not to drive or operate machinery if affected.

Precautions

- Tramadol Hydrochloride Injection 100mg/2ml should be used with caution in opioid -dependent patients, patients with head injury, a reduced level of consciousness of uncertain origin, disorders of the respiratory centre or function, increased intracranial pressure, severe impairment of hepatic and renal function and in patients prone to convulsive disorders or in shock. In patients sensitive to opiates the product should only be used with caution.
- Convulsions have been reported at therapeutic doses and the risk may be increased at doses exceeding the usual upper daily dose limit (400mg). Patients with a history of epilepsy or those susceptible to seizures should only be treated with tramadol if there are compelling reasons.
- The risk of convulsions may increase in patients taking tramadol and concomitant medication that can lower the seizure threshold.
- Care should be taken when treating patients with respiratory depression, or if concomitant CNS depressant drugs are being administered, or if the recommended dosage is significantly exceeded, as the possibility of respiratory depression cannot be excluded in these situations. At therapeutic doses respiratory depression has infrequently been reported.
- This medicinal product contains approximately 8.29mg sodium acetate trihydrate (1.4mg sodium) per 2ml dose.

4.5 Interaction with other medicinal products and other forms of interaction:

Tramadol Hydrochloride Injection 100mg/2ml should not be combined with MAO inhibitors.

In patients treated with MAO inhibitors in the 14 days prior to the use of the opioid pethidine, life-threatening interactions on the central nervous system, respiratory and cardiovascular function have been observed. The same interactions with MAO inhibitors cannot be ruled out during treatment with Tramadol Hydrochloride Injection 100mg/2ml.

Concomitant administration of Tramadol Hydrochloride Injection 100mg/2ml with other centrally acting drugs, including alcohol, may potentiate CNS depressant effects.

Tramadol can induce convulsions and increase the potential for selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, antipsychotics and other seizure threshold-lowering medicinal products (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions.

Theoretically there is a possibility that tramadol could interact with lithium. There have been no reports of this potential interaction.

Concomitant therapeutic use of tramadol and serotonergic drugs, such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors, tricyclic antidepressants and mirtazapine may cause serotonin toxicity. Serotonin syndrome is likely when one of the following is observed:

- Spontaneous clonus
- Inducible or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature > 38 °C and inducible or ocular clonus.

Withdrawal of the serotonergic drugs usually brings about a rapid improvement. Treatment depends on the type and severity of the symptoms.

There have been isolated reports of interaction with coumarin anticoagulants resulting in an increased INR with major bleeding and ecchymoses in some patients and so care should be taken when commencing treatment with tramadol in patients on anticoagulants.

Pharmacokinetic studies were conducted to investigate the effects of cimetidine, quinidine and carbamazepine on the pharmacokinetics of tramadol.

Carbamazepine – The simultaneous administration of carbamazepine markedly decreases serum concentrations of tramadol to an extent that a decrease in analgesic effectiveness and a shorter duration of action may occur.

Cimetidine - With the concomitant or previous administration of cimetidine clinically relevant interactions are unlikely to occur. Therefore no alteration of the tramadol dosage regimen is recommended for patients receiving chronic cimetidine therapy.

Quinidine - A study in 12 healthy volunteers has shown that quinidine causes an approximate 25% increase in the tramadol C_{max} and AUC; T_{max} is unaffected. However, the increases in C_{max} and AUC fall within the normal therapeutic range for tramadol, and no dosage adjustment is required.

Other active substances known to inhibit CYP3A4, such as ketoconazole and erythromycin, might inhibit the metabolism of tramadol (N-demethylation) probably also the metabolism of the active O-

demethylated metabolite. The clinical importance of such an interaction has not been studied.

In a limited number of studies the pre- or postoperative application of the antiemetic 5-HT3 antagonist ondansetron increased the requirement of tramadol in patients with postoperative pain.

4.6 Pregnancy, Breast-feeding and Fertility

Pregnancy

There is inadequate evidence available on the safety of tramadol in human pregnancy. Therefore tramadol should not be used in pregnant women.

Tramadol - administered before or during birth - does not affect uterine contractility. In neonates it may induce changes in the respiratory rate which are usually not clinically relevant. Chronic use during pregnancy may lead to neonatal withdrawal symptoms.

Breast-feeding

During lactation about 0.1 % of the maternal dose is secreted into the milk. ZYDOL is not recommended during breast-feeding. After a single administration of tramadol it is not usually necessary to interrupt breast-feeding.

Fertility

Post marketing surveillance does not suggest an effect of tramadol on fertility. Animal studies did not show an effect of tramadol on fertility.

4.7 Effects on ability to drive and use machines

Tramadol Hydrochloride Injection 100mg/2ml may cause somnolence and dizziness and these effects may be potentiated by alcohol and other CNS depressants. Ambulant patients should be warned not to drive or operate machinery if affected.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

• The medicine is likely to affect your ability to drive

• Do not drive until you know how the medicine affects you

• It is an offence to drive while under the influence of this medicine

• However, you would not be committing an offence (called 'statutory defence') if:

- The medicine has been prescribed to treat a medical or dental problem and
- You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
- It was not affecting your ability to drive safely

4.8 Undesirable effects

The following Adverse Events have been reported:

Cardiovascular system disorders:

Uncommon: cardiovascular regulation (palpitation, tachycardia, postural hypotension or cardiovascular collapse). These adverse effects may occur especially after intravenous administration and in patients who are physically stressed.

Rare: bradycardia, increase in blood pressure.

Nervous system disorders:

Very common: dizziness.

Common: headache, somnolence.

Rare: changes in appetite, paraesthesia, tremor, respiratory depression, epileptiform convulsions, involuntary muscle contractions, abnormal coordination, syncope.

Not known: speech disorders.

If the recommended doses are considerably exceeded and other centrally depressant substances are administered concomitantly, respiratory depression may occur.

Psychiatric disorders:

Rare: hallucinations, confusion, sleep disturbance, anxiety and nightmares. These include changes in mood (usually elation, occasionally dysphoria), changes in activity (usually suppression, occasionally increase) and changes in cognitive and sensorial ability (e.g. decision behaviour, perception disorders). Dependence may occur.

Eye disorders:

Rare; blurred vision

Not known: mydriasis.

Respiratory system disorders:

Rare: dyspnoea.

Worsening of asthma has been reported, though a causal relationship has not been established.

Gastrointestinal disorders:

Very common: nausea.

Common: vomiting, constipation, dry mouth.

Uncommon: retching, gastrointestinal irritation (a feeling of pressure in the stomach, bloating), diarrhoea

Skin and subcutaneous disorders:

Common: sweating.

Uncommon: dermal reactions (e.g. pruritus, rash, urticaria).

Musculo-skeletal system disorders:

Rare: muscle weakness

4.9 Overdose

Symptoms:

In principle, on intoxication with tramadol symptoms similar to those of other centrally acting analgesics (opioids) are to be expected. These include in particular miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest.

Treatment:

The general emergency measures apply. Keep open the respiratory tract (aspiration!), maintain respiration and circulation depending on the symptoms. The antidote for respiratory depression is naloxone. In animal experiments naloxone had no effect on convulsions. In such cases diazepam should be given intravenously.

In case of intoxication orally, gastrointestinal decontamination with activated charcoal or by gastric lavage is only recommended within 2 hours after tramadol intake. Gastrointestinal decontamination at a later time point may be useful in case of intoxication with exceptionally large quantities.

Tramadol is minimally eliminated from the serum by haemodialysis or haemo-filtration. Therefore treatment of acute tramadol intoxication with haemodialysis or haemofiltration alone is not suitable for detoxification.

5. PHARMACOLOGICAL PROPERTIES :

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics – other opioids

ATC code: N 02A X02

Mechanism of action:

Tramadol is a centrally acting opioid analgesic. It is a non-selective pure agonist at μ, δ and κ opioid receptors with a higher affinity for the μ receptor. Other mechanisms which contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenalin and enhancement of serotonin release.

Tramadol has an antitussive effect. In contrast to morphine, analgesic doses of tramadol over a wide range have no respiratory depressant effect. Also gastrointestinal motility is less affected. Effects on the cardiovascular system tend to be slight. The potency of tramadol is reported to be 1/10 (one tenth) to 1/6 (one sixth) that of morphine.

5.2 Pharmacokinetic properties :

More than 90% of tramadol is absorbed after oral administration. The mean absolute bioavailability is approximately 70 %, irrespective of the concomitant intake of food. The difference between absorbed and non-metabolised available tramadol is probably due to the low first-pass effect. The first-pass effect after oral administration is a maximum of 30 %.

Tramadol has a high tissue affinity ($V_{d,ß}$= 203 ± 40 l). It has a plasma protein binding of about 20 %.

Following a single oral dose administration of tramadol 100 mg as capsules or tablets to young healthy volunteers, plasma concentrations were detectable within approximately 15 to 45 minutes within a mean C_{max} of 280 to 208 mcg/L and T_{max} of 1.6 to 2h.

Tramadol passes the blood-brain and placental barriers. Very small amounts of the substance and its O-desmethyl derivative are found in the breast-milk (0.1 % and 0.02 % respectively of the applied dose).

Elimination half-life $t_{1/2,ß}$ is approximately 6 h, irrespective of the mode of administration. In patients above 75 years of age it may be prolonged by a factor of approximately 1.4.

In humans tramadol is mainly metabolised by means of N- and O-demethylation and conjugation of the O-demethylation products with glucuronic acid. Only O-desmethyltramadol is pharmacologically active. There are considerable interindividual quantitative differences between the other metabolites. So far, eleven metabolites have been found in the urine.

Animal experiments have shown that O-desmethyltramadol is more potent than the parent substance by the factor 2 - 4. Its half-life $t_{1/2,\beta}$ (6 healthy volunteers) is 7.9 h (range 5.4 - 9.6 h) and is approximately that of tramadol.

The inhibition of one or both types of the isoenzymes CYP3A4 and CYP2D6 involved in the biotransformation of tramadol may affect the plasma concentration of tramadol or its active metabolite. Up to now, clinically relevant interactions have not been reported.

Tramadol and its metabolites are almost completely excreted via the kidneys. Cumulative urinary excretion is 90 % of the total radioactivity of the administered dose. In cases of impaired hepatic and renal function the half-life may be slightly prolonged. In patients with cirrhosis of the liver, elimination half-lives of 13.3 $\pm$ 4.9 h (tramadol) and 18.5 $\pm$ 9.4 h (O- desmethyltramadol), in an extreme case 22.3 h and 36 h respectively, have been determined. In patients with renal insufficiency (creatinine clearance < 5 ml/min) the values were 11 $\pm$ 3.2 h and 16.9 $\pm$ 3 h, in an extreme case 19.5 h and 43.2 h respectively.

Tramadol has a linear pharmacokinetic profile within the therapeutic dosage range.

The relationship between serum concentrations and the analgesic effect is dose-dependent, but varies considerably in isolated cases. A serum concentration of 100 - 300 ng/ml is usually effective.

Paediatric population

The pharmacokinetics of tramadol and O-desmethyltramadol after single-dose and multiple- dose oral administration to subjects aged 1 year to 16 years were found to be generally similar to those in adults when adjusting for dose by body weight, but with a higher between-subject variability in children aged 8 years and below. In children below 1 year of age, the pharmacokinetics of tramadol and O-desmethyltramadol have been investigated, but have not been fully characterized. Information from studies including this age group indicates that the formation rate of O-desmethyltramadol via CYP2D6 increases continuously in neonates, and adult levels of CYP2D6 activity are assumed to be reached at about 1 year of age. In addition, immature glucuronidation systems and immature renal function may result in slow elimination and accumulation of O-desmethyltramadol in children under 1 year of age.

5.3 Preclinical safety data :

Preclinical safety data does not add anything of further significance to the prescriber.

6.0 PHARMACEUTICAL PARTICULARS :

6.1 List of Excipients

Disodium Edetate, Hydrochloric Acid & Water for Injections.

6.2 Incompatibilites:

Not applicable

6.3 Shelf life:

36 Months

6.4 Special precaution for storage :

Store at a temperature below 30^{o}C. Protect from light.

6.5 Nature and contents of container :

Clear colourless liquid filled in 2ml clear USP type-I glass ampoule.

6.6 Special precautions for disposal and other handling:

For single use only. Discard any unused product at the end of each operating session.

7.0 Marketing authorisation holder:

Name	:	**Fexona pharmaceutical Co., Ltd**
Address	:	19, Akinlawon Street , Ijesha -surulere, Lagos, Nigeria
Country	:	Nigeria

8.0 Marketing authorisation numbers : Not Applicable

9.0 Date of the first authorisation or renewal : Not Applicable

10.0 Date of revision of the text : Not Applicable

11.0 Dosimetry (If Applicable) : Not Applicable

12.0 Instructions for Preparation of Radiopharmaceuticals (If Applicable) : Not Applicable

1.3.2 Labelling (Outer & Inner labels)

Enclosed

Carton Label:	
	Proprietary Name
1.	International Non-Proprietary name of the Active Pharmaceutical Ingredient
2.	Amount of Active Pharmaceutical Ingredient present in a dosage unit
3.	List of excipients
4.	Pharmaceutical form and contents of the container
5.	Method and route of administration
6.	Special warning
7.	Batch number
8.	The manufacturing date
9.	The expiry date
10.	Special storage conditions
11.	The name and address of the Marketing Authorization Holder in the EAC
12.	Physical address of the site responsible for release of the finished product
13.	General classification for distribution (Controlled Medicines)
14.	Dosage and Usage

1.3.3 Package Insert (PIL)

Enclosed

93 x 224 mm

93mm

224mm

FOR THE USE OF ONLY A REGISTERED MEDICAL/PHARMACY PRACTITIONER OR A HOSPITAL/LABORATORY

FEXONA® TRAMADOL INJECTION

Tramadol Hydrochloride Injection 100mg/2mL

Composition

Each 2mL contains:

Tramadol Hydrochloride	BP	100mg
Water for Injections	BP	q.s

Clinical Pharmacology

Fexona® Tramadol Injection contains tramadol, a cyclohexanol derivative, is a centrally acting analgesic, which possesses opioid agonist properties. Tramadol appears to modify the transmission of pain impulses by inhibition of monoamine reuptake. The analgesic activity of tramadol has been demonstrated in both animal models and human subjects. Tramadol also has an antitussive action but has no effect on gastrointestinal motility. At the recommended dosages, the effects of tramadol given parenterally on the respiratory and cardiovascular systems appear to be clinically insignificant

Pharmacokinetics

After administration, the mean absolute bioavailability after intramuscular administration was found to be 100%. The distribution of tramadol following intravenous administration is rapid and in two phases with different half-lives of 0.31 ± 0.17 hours (initial rapid phase) and 1.7 ± 0.4 hours (slower phase) respectively. After intravenous administration of 100 mg tramadol, the serum concentration was 613 ± 221 ng/ml at 15 minutes post dosing and 409 ± 79 ng/ml at 2 hours post dosing. Tramadol has a high tissue affinity with an apparent volume of distribution of 203 L after intravenous dosing in healthy volunteers. Tramadol undergoes hepatic metabolism with approximately 85% of an intravenous dose being metabolized in young healthy volunteers. Tramadol is biotransformed primarily by N- and O-demethylation and by glucuronidation of the O-demethylation products. Eleven metabolites have so far been identified in man. Only one metabolite, O-demethyl tramadol (M1), is pharmacologically active showing analgesic activity. Tramadol is essentially excreted via the kidneys. The mean elimination half-life of tramadol following intravenous administration is 5-6 hours. Total clearance of tramadol was 28.0 L/h following intravenous administration.

Indications and Usage

Fexona® Tramadol injection is used in symptomatic relief of moderateto severe pains.

Dosage and Administration

Route of administration: Intramuscular & intravenous injection.

Adults: A single dose of 50 or 100 mg 4-6 hourly is usually required. Intravenous injections must be given slowly over 2-3 minutes. In severe (post-operative) pain, an initial bolus of 100 mg is administered 10-20 minutes up to a total dose of 250 mg including the initial bolus. Subsequent doses should be 50 or 100 mg administered 4-6 hourly. If the administration of Tramadol injection has been forgotten, the pain may return. The dose should not be doubled. Administration should be continued as before. A total daily dose of 400 mg should not be exceeded except in special clinical circumstances.

Children aged 1 to 14 years: 1 to 2 mg tramadol hydrochloride per kg body weight as a single dose

Special warnings

At therapeutic doses, Tramadol has the potential to cause withdrawal symptoms. Rarely cases of dependence and abuse have been reported. Because of this potential the clinical need for continued analgesic treatment should be reviewed regularly. In patients with a tendency to drug or alcohol abuse or dependence, treatment should be for short periods and under strict medical supervision, because in these cases there is a risk of suicidal tendency. Tramadol Injection is not a suitable substitute in opioid dependent patients. The product does not suppress morphine withdrawal symptoms although it is an opioid agonist. Convulsions have been reported at therapeutic doses and the risk may be increased at doses exceeding the usual upper daily dose limit (400 mg tramadol). Patients with a history of epilepsy or those susceptible to seizures should only be treated with tramadol if there are compelling reasons. The risk of convulsions may increase in patients taking tramadol and concomitant medication that can lower the seizure threshold

Contraindications

Tramadol Injection should not be given to patients who have previously shown hypersensitivity to the product. The product should not be administered to patients suffering from acute intoxication with hypnotics, centrally acting analgesics, opioids, psychotropic drugs or alcohol. In common with other opioid analgesics, tramadol should not beadministered to patients who are receiving monoamine oxidase(MAO) inhibitors or within 2 weeks of their withdrawal. The product must not be used in epilepsy not adequately controlled by treatment.

Precautions

In patients with severe renal or hepatic impairment, head injury, increased intracranial pressure, or patients in shock or at risk of convulsions, Tramadol Injection should be used with caution. At present tramadol Injection should not be used during light planes of anaesthesia as enhanced intra-operative recall was reported in a study of the use of tramadol during anesthesia with enflurane and nitrous oxide.

At therapeutic doses of tramadol respiratory depression has been reported infrequently. Therefore care should be taken when administering Tramadol Injection to patients with existing respiratory depression or to patients taking concomitant CNS depressant drugs.

Side Effects

Most commonly, nausea and dizziness were reported. Common effects were headache, muzziness, constipation, dry mouth, vomiting and sweating. Uncommon effects include disorders of cardiovascular regulation (e.g. palpitation, tachycardia, postural hypotension up to cardiovascular collapse), further, retching and gastrointestinal irritation, or dermal reactions (e.g. pruritus, rash or urticaria). Rarely reported effects include bradycardia, muscle twitching, coordination disorders, temporary loss of consciousness - syncope, increase in blood pressure, change in appetite, paraesthesia, tremor, hallucinations, confusion sleep disorders and nightmares, changes in mood (usually elation, occasionally dysphonia), change in activity, change in cognitive and sensorial capacity (e.g. perception disorders), breathlessness (dyspnoea). Rare effects are also motorial weakness, blurred vision and micutition disorders.

Pregnancy and lactation

Sufficient evidence of the safety of tramadol during pregnancy in humans is not available. Therefore you should not use tramadol injection throughout pregnancy. The repeated use of tramadol injection during pregnancy may lead to habituation in the unborn child and as a result, the child may experience withdrawal symptoms after birth.

Lactation: Tramadol injection should not be administered during breast-feeding

Drug Interactions

Tramadol Injection may potentiate the CNS depressant effects of other centrally acting drugs (including alcohol, sedatives, sleeping pills and certain painkillers such as morphine and codeine) when administered concomitantly with such drugs. Tramadol may increase the potential for both selective serotonin re-uptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) to cause convulsions. Administration of tramadol Injection together with carbamazepine, pentazocine, nalbuphine or buprenorphine (painkillers), ondansetron results in markedly decreased serum concentrations of tramadol which may reduce analgesic effectiveness and shorten the duration of action. Changes in serum concentrations of tramadol have been associated with simultaneous dosing of cimetidine. Inhibitors of CYP3A4 (e.g. ketoconazole or erythromycin) may inhibit the tramadol metabolism

Effects on ability to drive and use machines

Tramadol injection may lead to dizziness, muzziness and blurred vision and therefore affect the patient's reactions. Patients should be warned not to drive a car or another vehicle, not to use electric tools or operate machinery and not to work without a firm hold, if affected.

Over dosage

Accidental administration of an additional dose of Tramadol injection usually has no negative effects. The next dose should be given as planned. After administration very high doses, pin-point pupils, vomiting, fall in blood pressure, fast heart-beat, feeling faint, reduced level of consciousness up to coma (deep unconsciousness), epileptic-like fits, and difficulty in breathing up to stoppage of breathing may occur.

Treatment of overdose requires the maintenance of the airway and cardiovascular functions. Respiratory depression may be reversed using naloxone and fits controlled with diazepam. The treatment of acute overdose of tramadol using haemodialysis or haemo filtration alone is not sufficient or suitable due to the slow elimination of tramadol from the serum by these routes

Shelf life: 36 months

Storage: Store at a temperature below 30°C. Protect from light.
Keep the medicine out of reach of children

Presentation: 10 x 2mL glass ampoules in plastic tray per box

NAFDAC Reg. No:

Manufactured by:
Psychotropics India Limited
Plot No.12&12A, Industrial Park –II,
Phase –I, Salempur, Mehdood-2
Haridwar-249403, (Uttarakhand) INDIA

Manufactured for:
Fexona Pharmaceutical Co., Ltd
19, Akinlawon Street, Ijesha-Surulere,
Lagos – Nigeria

1.4 Regional Summaries

1.4.1 Bioequivalence Information Form (BTIF)

Not Applicable

1.4.2 Quality Information Summary

1.5 Electronic review Documents

1.6 Samples