SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of medicinal product

TRD-Contin 100
(Controlled Release Tablets of Tramadol Hydrochloride)

2. Qualitative and Quantitative composition

Core Tablets

Name of Ingredient (S)	Reference Standard	Quantity (mg/tablet)	Function
Tramadol Hydrochloride	BP	100.00	Active
Lactose	BP/Ph.Eur.	50.00	Diluent
Cetostearyl Alcohol	BP/Ph.Eur.	37.00	Drug Release controlling agent
Ethyl Cellulose 10cps	USNF	20.00	Drug Release controlling agent
Ethyl Cellulose 50cps	USNF	5.00	Drug Release controlling agent
Talc	BP/Ph.Eur.	3.00	Glidant
Magnesium Stearate	BP/Ph.Eur.	2.00	Lubricant
Isopropyl Alcohol*	BP/Ph.Eur.	50.00	Solvent
Weight of the core tablet		217.00 mg	

*Lost during Processing. Not present in the final product.

Film Coating

Ingredient	Reference Standard	Quantity (mg/tablet)	Function
Opadry white 31F58914	IH.	8.00	Coating Material
Purified water*	Ph.Eur.	0.08 ml	Solvent
Weight of the film coated tablet		225.00 mg	

* Lost during processing. Not present in the final weight.

3. Pharmaceutical form

Controlled release tablets
Description: White, biconvex, scored, film-coated caplets of a controlled-release formulation engraved with 'MM' logo on one of the facets.

4. Clinical particulars

4.1 Therapeutic indications

For management of moderate to severe pain in adults.

4.2 Posology and method of administration

Adults:

One to two TRD-CONTIN 100 mg tablets twice daily (corresponding to 200 - 400 mg tramadol hydrochloride). The total daily dose should not exceed 400 mg of tramadol hydrochloride, except in special clinical circumstances.

Children

Safety and efficacy of TRD-CONTIN tablets in children has not been established. Therefore, use of TRD-CONTIN in the pediatric population is not recommended.

Elderly patients

In general, dose selection for an elderly patient should be cautious, usually starting at the lower end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy. In patients over 75 years of age, daily doses in excess of 300 mg are not recommended.

Renal insufficiency

In all patients with creatinine clearance less than 30 mL/min, a prolonged dosage interval should be taken into consideration, with a maximum daily dose of 200 mg.

Since only 7% of an administered dose is removed by hemodialysis of 4-hour duration, dialysis patients can receive their regular dose on the day of dialysis. The recommended dose for adult patients with cirrhosis is 50 mg every 12 hours.

Administration of tramadol is not related to food intake. TRD-CONTIN 100 Continus tablets should not be chewed or crushed. For dosage flexibility, TRD-CONTIN 100 Continus tablets may be broken into two equal halves along the score line indicated on each tablet.

4.3 Contraindications

Tramadol must not be taken in cases of:
- known hypersensitivity to tramadol or opioids;

- Acute intoxication with alcohol, hypnotics, analgesics, opioids and psychoactive substances;

- concurrent administration of monoamine oxidase inhibitors or within two weeks of their withdrawal;

- epilepsy, which cannot be adequately controlled by treatment

TRD-CONTIN must not be used for narcotics substitution.

TRD-CONTIN tablets are not recommended for use in children.

4.4 Warnings and Precautions

Tramadol must only be administered after thorough consideration of risks versus benefits and appropriate precautions in cases of:
- opioid dependency;

- impaired consciousness of unknown origin, shock;

- disorders of the respiratory centre and respiratory dysfunction;

- states of increased intracranial pressure in case of head injuries or cerebral diseases;

- impaired hepatic or renal function;

- acute abdominal conditions

Tramadol is not suited for patients with rare hereditary galactose intolerance, lapp lactase deficiency or glucose/galactose malabsorption.

The intake of recommended doses of tramadol has been reported to be associated with seizures. There may be an increased risk at doses exceeding the maximum recommended daily dose (400 mg). The concomitant use of drugs lowering the seizure threshold may also increase the risk of convulsions. Patients with a history of epilepsy or those susceptible to seizures should be treated with tramadol only for compelling reasons.

Tramadol has a low potential for drug dependency. Prolonged use may result in tolerance, mental or physical dependency. In patients with a tendency to medicinal drug abuse or dependency, treatment with tramadol should be done under strict medical supervision.

Tramadol is not suitable as a substitute in opioids-dependent patients. Although tramadol is an opioids agonist, it cannot suppress morphine withdrawal symptoms.

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

Use with Central Nervous System Depressants

Tramadol should be used with caution and in reduced dosages when administered to patients receiving CNS depressants such as alcohol, opioids, anesthetic agents, narcotics, phenothiazines, tranquilizers or sedative hypnotics. Tramadol increases the risk of CNS and respiratory depression in these patients.

Use with Seizure Threshold Lowering Drugs

Risk of seizures may increase with concomitant use of selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), other opioids, monoamine oxidase (MAO) inhibitors, neuroleptics or other drugs that reduce the seizure threshold.

Use with Carbamazepine

Patients taking Carbamazepine may have a significantly reduced analgesic effect of tramadol. Because Carbamazepine increases tramadol metabolism and because of the seizure risk associated with tramadol, concomitant administration of tramadol and Carbamazepine is not recommended.

Use with Quinidine

Concomitant administration of quinidine and tramadol results in increased concentrations of tramadol and reduced concentrations of M1. The clinical consequences of these findings are unknown.

Use with Inhibitors of CYP2D6

In vitro drug interaction studies in human liver microsomes indicate that concomitant administration with inhibitors of CYP2D6 such as fluoxetine, paroxetine, and amitriptyline could result in some inhibition of the metabolism of tramadol.

Use with Cimetidine

Concomitant administration of tramadol with cimetidine does not result in clinically significant changes in tramadol pharmacokinetics. Therefore, no alteration of the dosage regimen is recommended.

Use with MAO Inhibitors

Concomitant use of tramadol with MAO inhibitors or SSRIs increases the risk of adverse events, including seizures and serotonin syndrome.

Use with Digoxin and Warfarin

Post-marketing surveillance has revealed rare reports of digoxin toxicity and alteration of Warfarin effect, including elevation of prothrombin times.

4.6 Pregnancy and lactation

Pregnancy Category C: The safety of tramadol in pregnancy and lactation has not been established. Therefore, tramadol should only be used in pregnancy when potential benefit outweighs the risk.

Tramadol is excreted in very small amounts (approximately 0.1 % of an intravenous dose) in human breast milk. Tramadol should, therefore, not be used during breast-feeding. A single administration of tramadol does not usually require interruption of the lactation period.

4.7 Effects on ability to drive and use machines.
Tramadol may impair physical or mental ability required for performance of skilled work and for performance of potentially hazardous tasks like driving, operating machinery, etc.

4.8 Undesirable effects
The most frequent undesirable effects occurring during treatment with tramadol are nausea and dizziness, which occur in one out of 10 patients.
Cardiovascular system:
Uncommon (0.1 – 1 %): Effects on cardiovascular regulation (palpitation, increased heartbeat, fainting spells and circulatory collapse). These adverse effects may occur especially in an upright position and in the presence of physical stress.
Rare (0.01 - 0.1 %): Bradycardia (reduced heart rate), increased blood pressure.
Central nervous system: Very common (>10 %): Dizziness
Common (1 – 10 %): Headache, drowsiness.
Rare (0.01 - 0.1 %): Changes in appetite, paraesthesia, tremor, respiratory depression, epileptiform seizures.
If the recommended doses are exceeded or given concomitantly with other medicinal drugs with a centrally depressing effect, respiratory depression may occur.
Epileptiform convulsions occurred mainly after administration of high doses of tramadol or after the concomitant administration of medicinal drugs which themselves may have a seizure-inducing effect or which lower seizure threshold.
Psychological:
Rare (0.01 - 0.1 %): Hallucination, state of confusion, sleeping disorders, nightmares. Mental complaints may occur after treatment with tramadol; depending on personality and duration of treatment their intensity and nature may vary from case to case. They may include mood swings (usually elation, occasionally dysphoria) and changes in cognitive and sensory capacity (changes in sensory perception and cognition, which may result in erroneous decision behavior). Dependency may occur.
Sensory organs:
Rare (0.01 - 0.1 %): Blurred vision
Respiratory organs: Although respiratory depression and deterioration of asthma have been reported, a causal relationship with the active substance tramadol could not be established.
Gastrointestinal tract: Very common (> 10 %): Nausea
Common (1 – 10 %): Vomiting, constipation, dryness of the mouth.
Uncommon (0.1 – 1 %): Retching, diarrhoea, gastrointestinal complaints (Feeling of pressure in the stomach, sensation of Fullness).
Skin and accessory organs: Common (1 – 10 %): Sweating
Uncommon (0.1 – 1 %): Skin reactions (e.g. itching, rash, flush)
Locomotor system: Rare (0.01 - 0.1 %): Reduced muscular strength
Liver, gall bladder: Very rare (< 0.01%): Increased transaminases
Kidneys: Rare (0.01 - 0.1 %): Micturition disorders
General condition: Rare (0.01 - 0.1 %): Allergic reactions (e.g. respiratory distress, “whistling” breathing sounds, swelling) and anaphylaxis have occurred in very rare cases.
If tramadol is taken over a prolonged period of time, dependency may occur, even if the risk is low. Abrupt discontinuation of the medication may cause withdrawal symptoms:

agitation, anxiety, nervousness, sleeping disorders, hyperkinesia, tremor and gastrointestinal symptoms. Clinical experience suggests that withdrawal symptoms may be relieved by reinstitution of opioid therapy followed by a gradual, tapered dose reduction of the medication combined with symptomatic support.

4.9 Overdose & Its Treatment

Symptoms

In case of intoxication with tramadol, symptoms are to be expected as with other centrally active analgesics (opioids), especially miosis, vomiting, cardiovascular collapse, impaired consciousness up to comatose state, spasms and respiratory depression up to respiratory paralysis, possibly with fatal outcome.

Management

Supportive measures such as clearing the airways (aspiration), maintaining respiratory and cardiovascular function should be asserted, depending on the symptoms; naloxone is used to reverse respiratory depression. Animal experiments have proved naloxone to be ineffective in case of spasms, for which, use of intravenous diazepam is recommended.

Tramadol is only slightly dialyzable. Therefore, treatment of acute intoxication by haemodialysis or haemofiltration alone, is not suitable.

5.0 Pharmacological properties

5.1 Pharmacodynamic properties

Tramadol is a centrally acting synthetic opioid analgesic. Although its mode of action is not completely understood, at least two complementary mechanisms appear applicable: binding of parent drug and its M1 metabolite to μ-opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin. The analgesic activity of tramadol is due to both the parent drug and the M1 metabolite. Tramadol is administered as a racemate and both the [-] and [+] forms of both tramadol and M1 metabolite are detected in the circulation.

5.2 Pharmacokinetic properties

It is well absorbed orally with an absolute bioavailability of 75%. It has a volume of distribution of approximately 2.7L/kg and is only 20% bound to plasma proteins. Tramadol is extensively metabolized by a number of pathways, including CYP2D6 and CYP3A4, as well as by conjugation of the parent drug and its metabolites. The M1 metabolite is pharmacologically active in animal models. Tramadol and its metabolites are excreted primarily in the urine with observed plasma half-lives of 6.3 and 7.4 hours for tramadol and M1, respectively. Linear pharmacokinetics have been observed following multiple doses of 50 and 100 mg to steady state.

5.3 Preclinical Safety Data

In single and repeat dose toxicity studies (rodents and dogs) exposure to tramadol 10 times that expected in man is required before toxicity (hepatoxicity) is observed.

Symptoms of toxicity are typical of opioids and include restlessness, ataxia, vomiting, tremor, dyspnoea and convulsions.

Exposure to tramadol (greater than that expected in man) in lifetime toxicity studies in rodents did not reveal any evidence of carcinogenic hazard, and a variety of *in vitro* and *in vivo* mutagenicity tests were negative.

6.0 Pharmaceutical particulars

6.1 List of Excipients

S.No.	Name of the Excipients
1.	Lactose
2.	Cetostearyl Alcohol
3.	Ethyl Cellulose 10 CPS
4.	Ethyl Cellulose 50 CPS
5.	Purified Talc
6.	Magnesium Stearate
7.	Isopropyl Alcohol
8.	Opadry white 31F58914
9.	Purified water

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

2 years (24 months)

6.4 Special precautions for storage

Store at or below 30°C, in a dry place, protected from light.

6.5 Nature and content of container

TRD-Contin 100 Tablets are packaged in blister strips comprising of PVDC coated opaque white PVC Film (66mm/0.250mm) backed with aluminium foil (62mm/0.025mm).

Box of 50 Tablets (5x10's blister strips)

6.6 Instructions for use/handling

Keep out of reach of children,

The tablets should be swallowed whole and not chewed.

7. Name and address of marketing authorization holder

Manufactured by:
Modi-Mundipharma Pvt. Ltd.
Modipuram – 250 110,
U.P., India
Phone: +91-121-2576214-17
Fax: +91-121-2575517

Registered by:
Modi-Mundipharma Pvt. Ltd.
1400, Modi Tower,
98, Nehru Place,
New Delhi – 110019, India.
Phone: +91-11-42504555
Fax: +91-11-26451659

8. Marketing authorization number

Rwanda FDA-HMP-MA-1946

9. Date of first authorization/renewal of the authorization

01/09/2024

10. Date of (partial) revision of the text

December 2024