SUMMARY OF PRODUCT CHARACTERISTICS

TDRONA FORTE

(PARACETAMOL AND TRAMADOL HYDROCHLORIDE TABLETS)

1. NAME OF THE MEDICINAL PRODUCT : TDRONA FORTE

Generic Name of Product **:** PARACETAMOL AND TRAMADOL HYDROCHLORIDE TABLETS

Strength (formula) **:** Each Uncoated tablet contains:

Paracetamol BP 500mg
Tramadol Hydrochloride BP 50mg
Excipients q.s.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

2.1 Qualitative & Quantitative Composition Declaration:

Sr. No.	Ingredients.	Specification	Qty/Tab mg.	% O.A.	Std. Qty. kg	Reason for inclusion
DRY MIXING						
1.	Paracetamol	BP	500.0	--	150.00	Active Ingredient
2.	Tramadol HCl	BP	50.00	--	15.00	Active ingredient
3.	Maize starch	BP	112.16		33.65	Diluent
4.	Microcrystalline cellulose	BP	60.00		18.00	Diluent
5.	Colour Tartrazine Supra	IHS	4.00		1.200	Colorant
BINDER PREPARATION						
6.	PVP K-30	BP	6.00		1.800	Binder
7.	Maize starch	BP	32.00		9.600	Binder
8.	Sodium Methyl Paraben BP	BP	0.75		0.225	Preservative
9.	Sodium Propyl Paraben BP	BP	0.075		0.025	Preservative
10.	Purified Water	BP	Q.S.		Q.S.	Vehicle
LUBRICATION						
11.	Colloidal silicon dioxide	BP	2.00	--	0.600	Glidant
12.	Purified Talc	BP	10.00	--	3.00	Glidant
13.	Sodium Starch Glycolate	BP	20.00	--	6.00	Super disintegrant

14.	Magnesium Stearate	BP	3.000	----	0.90	Lubricant
Avg. Wt. of Tablet			800.00 mg			

3. PHARMACEUTICAL FORM:

Yellow colored capsule shaped uncoated tablets, having break line on one side and plain on other side.

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications:

Tramadol hydrochloride/Paracetamol tablets are indicated for the symptomatic treatment of moderate to severe pain.

The use of Tramadol hydrochloride/Paracetamol should be restricted to patients whose moderate to severe pain is considered to require a combination of tramadol and paracetamol.

4.2 Posology and Method of Administration:

Posology

Adults and adolescents (12 years and older)

The use of Tramadol hydrochloride/Paracetamol should be restricted to patients whose moderate to severe pain is considered to require a combination of tramadol and paracetamol.

The dose should be individually adjusted according to intensity of pain and response of the patient.

An initial dose of two tablets of Tramadol hydrochloride/Paracetamol is recommended. Additional doses can be taken as needed, not exceeding 8 tablets (equivalent to 300 mg tramadol and 2600 mg paracetamol) per day.

The dosing interval should not be less than six hours.

Tramadol hydrochloride/Paracetamol should under no circumstances be administered for longer than is strictly necessary. If repeated use or long term treatment with Tramadol hydrochloride/Paracetamol is required as a result of the nature and severity of the illness, then careful, regular monitoring should take place (with breaks in the treatment, where possible), to assess whether continuation of the treatment is necessary.

Children

The effective and safe use of Tramadol hydrochloride/Paracetamol has not been established in children below the age of 12 years. Treatment is therefore not recommended in this population.

Elderly patients

The usual dosages may be used although it should be noted that in volunteers aged over 75 years the elimination half life of tramadol was increased by 17% following oral administration. In patients over 75 years old, it is recommended that the minimum interval between doses should be not less than 6 hours, due to the presence of tramadol.

Renal insufficiency

Because of the presence of tramadol, the use of Tramadol hydrochloride/Paracetamol is not recommended in patients with severe renal impairment (creatinine clearance < 10 ml/min). In cases of moderate renal impairment (creatinine clearance between 10 and 30 ml/min), the dosing should be increased to 12-hourly intervals. As tramadol is removed only very slowly by haemodialysis or by haemofiltration, post dialysis administration to maintain analgesia is not usually required.

Hepatic insufficiency

In patients with severe hepatic impairment Tramadol hydrochloride/Paracetamol should not be used. In moderate cases prolongation of the dosage interval should be carefully considered.

Method of Administration:

Oral administration

4.3 Contra – Indications:

Hypersensitivity to paracetamol or any of the other constituents.

Acute intoxication with alcohol, hypnotic drugs, centrally-acting analgesics, opioids or psychotropic drugs.

Tramadol hydrochloride/Paracetamol should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal

4.4 Special Warning and Precautions for Use:

The maximum dose of 8 tablets of Tramadol hydrochloride/Paracetamol should not be exceeded in adults and adolescents 12 years and older. In order to avoid inadvertent overdose, patients should be advised not to exceed the recommended dose and not to use any other paracetamol (including over the counter) or tramadol hydrochloride containing products concurrently without the advice of a physician.

In severe renal impairment (Creatinine clearance <10 ml/mm), Tramadol hydrochloride/Paracetamol is not recommended.

In patients with severe hepatic impairment Tramadol hydrochloride/Paracetamol should not be used . The hazards of paracetamol overdose are greater in patients with non-cirrhotic alcoholic liver disease. In moderate cases prolongation of dosage interval should be carefully considered.

In severe respiratory impairment, Tramadol hydrochloride/Paracetamol is not recommended.

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

4.5 Interaction with other medicinal products and other forms of interaction

- *Non-selective MAO Inhibitors*: risk of serotoninergic syndrome (diarrhoea, tachycardia, sweating, trembling, confusion, even coma).
- *Selective-A MAO Inhibitors*: extrapolation from non-selective MAO inhibitors, risk of serotoninergic syndrome (diarrhoea, tachycardia, sweating, trembling, confusion, even coma).
- *Selective-B MAO Inhibitors*: central excitation symptoms evocative of a serotoninergic syndrome (diarrhoea, tachycardia, sweating, trembling, confusion, even coma).

In case of recent treatment with MAO inhibitors, a delay of two weeks should occur before treatment with tramadol.

4.6 Pregnancy and lactation

Pregnancy

Since Tramadol hydrochloride/Paracetamol is a fixed combination of active ingredients including tramadol, it should not be used during pregnancy.

Paracetamol

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosage, but patients should follow the advice of their doctor regarding its use.

Tramadol

There are no adequate data from the use of tramadol in pregnant women. Tramadol crosses the placental barrier and chronic use during pregnancy can cause withdrawal symptoms in the new-born baby. Therefore, it should not be used during pregnancy.

Tramadol administered before or during birth does not affect uterine contractility. In neonates it may induce changes in respiratory rate which are not usually clinically relevant.

Lactation

Since Tramadol hydrochloride/Paracetamol is a fixed combination of active ingredients including tramadol, it should not be ingested during breast feeding.

Paracetamol

Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data on paracetamol does not contraindicate it for breast feeding.

Tramadol

Tramadol and its metabolites are found in small amounts in human breast milk. An infant could ingest 0.1% of the dose given to the mother. Tramadol hydrochloride should not be administered during breast feeding.

4.7 Effects on ability to drive and use machine:

Tramadol may cause drowsiness or dizziness, which may be enhanced by alcohol or other CNS depressants. If affected, the patient should not drive or operate machinery.

4.8 Undesirable effects

The most commonly reported undesirable effects during the clinical trials performed with the paracetamol/tramadol combination were nausea, dizziness and somnolence, observed in more than 10% of the patients.

Cardiac disorders:

- Uncommon: hypertension, palpitations, tachycardia, arrythmia.

Nervous system disorders:

- Very common: dizziness, somnolence
- Common: headache trembling
- Uncommon: involuntary muscular contractions, paraesthesia, tinnitus
- Rare: ataxia, convulsions.

Psychiatric disorders:

- Common: confusion, mood changes (anxiety, nervousness, euphoria), sleep disorders
- Uncommon: depression, hallucinations, nightmares, amnesia
- Rare: drug dependence.

4.9 Overdoses:

Tramadol hydrochloride/Paracetamol is a fixed combination of active ingredients. In case of overdose, the symptoms may include the signs and symptoms of toxicity of tramadol or paracetamol or of both these active ingredients.

Symptoms of overdose from tramadol

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.

Symptoms of overdose from paracetamol

An overdose is of particular concern in young children. Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalophathy, coma and death. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Liver damage is possible in adults who have taken 7.5-10 g or more of paracetamol. It is considered that excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested), become irreversibly bound to liver tissue.

Emergency treatment

- Transfer immediately to a specialised unit.
- Maintain respiratory and circulatory functions.
- Prior to starting treatment, a blood sample should be taken as soon as possible after overdose in order to measure the plasma concentration of paracetamol and tramadol and in order to perform hepatic tests.
- Perform hepatic tests at the start (of overdose) and repeat every 24 hours. An increase in hepatic enzymes (ASAT, ALAT) is usually observed, which normalizes after one or two weeks.
- Empty the stomach by causing the patient to vomit (when the patient is conscious) by irritation or gastric lavage.
- Supportive measures such as maintaining the patency of the airway and maintaining cardiovascular function should be instituted; naloxone should be used to reverse respiratory depression; fits can be controlled with diazepam.
- Tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration. Therefore treatment of acute intoxication with Tramadol hydrochloride/Paracetamol with haemodialysis or haemofiltration alone is not suitable for detoxification.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other opioids, ATC code: N02AX52.

Analgesics

Tramadol is an opioid analgesic that acts on the central nervous system. Tramadol is pure non selective agonists of the μ, δ, and κ opioid receptors with a higher affinity for the μ receptors. Other mechanisms which contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release. Tramadol has an antitussive effect. Unlike morphine, a broad range of analgesic doses of tramadol has no respiratory depressant effect. Similarly, the gastro-intestinal motility is not modified. The cardiovascular effects are generally slight. The potency of tramadol is considered to be one-tenth to one-sixth that of morphine.

The precise mechanism of the analgesic properties of paracetamol is unknown and may involve central and peripheral effects.

Tramadol hydrochloride/Paracetamol is positioned as a step II analgesic in the WHO pain ladder and should be utilised accordingly by the physician.

5.2 Pharmacokinetic properties

Tramadol is administered in racemic form and the [-] and [+] forms of tramadol and its metabolite M1, are detected in the blood. Although tramadol is rapidly absorbed after administration, its absorption is slower (and its half-life longer) than that of paracetamol.

After a single oral administration of a tramadol/paracetamol (37.5 mg/325 mg) tablet, peak plasma concentrations of 64.3/55.5 ng/ml [(+)-tramadol/(-)-tramadol] and 4.2 µg/ml (paracetamol) are reached after 1.8 h [(+)-tramadol/(-)-tramadol] and 0.9 h (paracetamol) respectively. The mean elimination half-lives $t_{1/2}$ are 5.1/4.7 h [(+)-tramadol/(-)-tramadol] and 2,5 h (paracetamol).

During pharmacokinetic studies in healthy volunteers after single and repeated oral administration of Tramadol hydrochloride/Paracetamol, no clinical significant change was observed in the kinetic parameters of each active ingredient compared to the parameters of the active ingredients used alone.

Absorption

Racemic tramadol is rapidly and almost completely absorbed after oral administration. The mean absolute bioavailability of a single 100 mg dose is approximately 75%. After repeated administration, the bioavailability is increased and reaches approximately 90%.

After administration of Tramadol hydrochloride/Paracetamol, the oral absorption of paracetamol is rapid and nearly complete and takes place mainly in the small intestine. Peak plasma concentrations of paracetamol are reached in one hour and are not modified by concomitant administration of tramadol.

The oral administration of Tramadol hydrochloride/Paracetamol with food has no significant effect on the peak plasma concentration or extent of absorption of either tramadol or paracetamol so that Tramadol hydrochloride/Paracetamol can be taken independently of meal times.

Distribution

Tramadol has a high tissue affinity ($V_{d,\beta}$=203 ± 40 l). It has a plasma protein binding of about 20%.
Paracetamol appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0.9 l/kg. A relative small portion (~20%) of paracetamol is bound to plasma proteins.

Metabolism

Tramadol is extensively metabolized after oral administration. About 30% of the dose is excreted in urine as unchanged drug, whereas 60% of the dose is excreted as metabolites.
Tramadol is metabolised through *O*-demethylation (catalysed by the enzyme CYP2D6) to the metabolite M1, and through*N*-demethylation (catalysed by CYP3A) to the metabolite M2. M1 is further metabolised through N-demethylation and by conjugation with glucuronic acid. The plasma elimination half-life of M1 is 7 hours. The metabolite M1 has analgesic properties and is more potent than the parent drug. The plasma concentrations of M1 are several-fold lower than those of tramadol and the contribution to the clinical effect are unlikely to change on multiple dosing.

Paracetamol is principally metabolized in the liver through two major hepatic routes: glucuronidation and sulphation. The latter route can be rapidly saturated at doses above the therapeutic doses. A small fraction (less than 4%) is metabolized by cytochrome P450 to an active intermediate (the N-acetyl benzoquinoneimine) which, under normal conditions of use, is rapidly detoxified by reduced glutathione and excreted in urine after conjugation to cysteine and mercapturic acid. However, during massive overdose, the quantity of this metabolite is increased.

Elimination

Tramadol and its metabolites are eliminated mainly by the kidneys.

The half-life of paracetamol is approximately 2 to 3 hours in adults. It is shorter in children and slightly longer in the newborn and in cirrhotic patients. Paracetamol is mainly eliminated by dose-dependent formation of glucuro- and sulpho-conjugate derivatives. Less than 9% of paracetamol is excreted unchanged in urine. In renal insufficiency, the half-life of both compounds is prolonged.

5.3 Preclinical safety data

Not available

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients

Maize starch, Microcrystalline cellulose, PVP K-30, Sodium methyl paraben, Sodium propyl paraben, Sodium starch glycolate, Purified talc, Aerosil, Magnesium stearate, Purified water, Tartrazine Supra.

6.2 Incompatibilities:

Not Applicable.

6.3 Shelf – life:

36 Months.

6.4 Special Precautions for Storage:

Store in a dry place below 25°C.

6.5 Nature and Contents of Container:

10 x 1 x 10 Tablets pack

6.6 Special Precautions for disposal:

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorization holder

Applicant:

Name: RONAK EXIM PRIVATE LIMITED
Address: Sant Kabir Road, Behind Gendi Gate,
Police Station, Baroda – 390 001,
GUJARAT
Country: INDIA
E-mail: ahmedi@ronakoverseas.com

Manufacturer:

Name: BADDER SCHULZ LABORATORIES

Address: Plot No. J-6,OIDC,Mahatma Gandhi
Udyog Nagar, Dabhel, Daman-396210, INDIA

8. FDA Application Number

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9. Date of Registration / Renewal of registration

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10. Date of revision of the text

Not applicable