PATIENT INFORMARION LEAFLET: INFORMATION FOR THE USER

PARAEFFER-TRAM

(Soluble Paracetamol BP 325 mg & Tramadol Hydrochloride BP 37.5 mg Tablet)

Read all of this leaflet carefully before you start PARAEFFER-TRAM using

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

In this leaflet:

1. WHAT PARAEFFER-TRAM AND WHAT IT IS USED FOR

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.

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.

2. BEFORE YOU TAKE PARAEFFER-TRAM

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.

3. HOW TO TAKE YOUR MEDICINE

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. POSSIBLE SIDE 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.

5. HOW TO STORE PARAEFFER-TRAM

Store in a dry place below 30°C. Protect from light, heat & moisture.
KEEP MEDICINES OUT OF REACH AND SIGHT OF CHILDREN.

6. FURTHER INFORMATION

What PARAEFFER-TRAM contains:

- The active pharmaceutical ingredient(s) are
- Paracetamol
- Tramadol Hydrochloride

The other ingredient(s) are
Sodium bicarbonate
Citric Acid Anhydrous
PVPK-30
Sodium Saccharine
Purified Water
Sodium bicarbonate Anhydrous
Simethicone
Tween-80
Isopropyl Alcohol
Sodium carbonate
Aspartame
Sodium Benzoate
Orange Flavor
PEG-8000

What PARAEFFER-TRAM looks like and contents of the pack: White to off white round, beveled edged, flat tablet, with orange odor.

3 x 4 Tablets in Alu-Alu Strip pack.

Manufacturer

Company Name	:	RONAK EXIM PRIVATE LIMITED
Address	:	OPP Ranoli Railway Station, Near GACL Plant Vadodara, Gujarat.
Country	:	INDIA
Phone	:	+91-265-242 8444
Fax	:	+91-265-243 8444
E-mail	:	ahmedi@ronakoverseas.com

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RONAK EXIM PVT. LTD. INDIA