Summary Product Characteristic for Pharmaceutical Product

1. Name of Medicinal Product

Traloget Plus (Tramadol HCl + Paracetamol) Tablets 37.5mg + 325mg

2. Qualitative and Quantitative Composition

Each film-coated tablet contains Tramadol HCl USP... 37.5mg and Paracetamol USP... 325mg

3. Pharmaceutical Form

Green colored, oval shaped film coated tablet, engraved "GP" on one side and plain on other side.

4. Clinical Particulars

4.1 Indications

Traloget Plus (Tramadol HCl + Paracetamol) Tablets are indicated for the symptomatic treatment of moderate to severe pain. The use of Traloget Plus (Tramadol HCl + Paracetamol) should be restricted to patients whose moderate to severe pain is considered to require a combination of tramadol HCl and paracetamol.

4.2 Posology and method of administration

Adults and Adolescents (12 years and older)
The dose should be individually adjusted according to intensity of pain and response of the patient. An initial dose of two tablets of Traloget Plus (Tramadol HCl + Paracetamol) is recommended. Additional doses can be taken as needed, not exceeding 8 tablets (equivalent to 300mg tramadol HCl and 2600mg paracetamol) per day. The dosing interval should not be less than six hours.

Special 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 HCl 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 HCl.

Renal Insufficiency

In cases of moderate renal insufficiency (creatinine clearance between 10 and 30 ml/min), the dosing should be increased to 12 hourly intervals. As tramadol HCl is removed only very slowly by hemodialysis or by hemofiltration, post dialysis administration to maintain analgesia is not usually required.

Hepatic Insufficiency

In patients with severe hepatic impairment Traloget Plus (Tramadol HCl + Paracetamol) should not be used. In moderate cases prolongation of the dosage interval should be carefully considered.

Children

The effective and safe use of Traloget Plus (Tramadol HCl + Paracetamol) has not been established in children below the age of 12 years. Treatment is therefore not recommended in this population.

4.3 Contra-indications

Tramadol HCl + Paracetamol is contraindicated in:

- Patients with known hypersensitivity to tramadol HCl or paracetamol or to any of the excipient of the product.
- Acute intoxication with alcohol, hypnotic drugs, centrally-acting \ analgesics, opioids or psychotropic drugs.
- Patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal.
- Severe hepatic impairment.
- Severe renal insufficiency (creatinine clearance <10ml/min).
- Epilepsy not controlled by treatment.

4.4 Special warnings and special precautions for use

- The hazards of paracetamol overdose are greater in patients with noncirrhotic alcoholic liver disease. In moderate cases prolongation of dosage interval should be carefully considered.
- In severe respiratory insufficiency, tramadol HCl + paracetamol is not recommended.
- Tramadol HCl is not suitable as a substitute in opioid-dependent patients. Although it is an opioid agonist, tramadol HCl cannot suppress morphine withdrawal symptoms.
- Convulsions have been reported in tramadol HCl treated patients susceptible to seizures or taking other medications that lower the seizure threshold, especially selective serotonin re-uptake inhibitors, tricyclic antidepressants, antipsychotics, centrally acting analgesics or local anesthesia. Epileptic patients controlled by a treatment or patients susceptible to seizures should

be treated with tramadol HCl + paracetamol only if there are compelling circumstances. Convulsions have been reported in patients receiving tramadol HCl at the recommended dose levels. The risk may be increased when doses of tramadol HCl exceed the recommended upper dose limit.

- Concomitant use of opioid agonists-antagonists (nalbuphine, buprenorphine, pentazocine) is not recommended.
- Tolerance and physical and/or psychological dependence may develop, even at therapeutic doses. The clinical need for analgesic treatment should be reviewed regularly. In opioid-dependent patients and patients with a history of drug abuse or dependence, treatment should only be for short period and under medical supervision.
- Tramadol HCl + paracetamol should be used with caution in patients with cranial trauma, in patients prone to convulsive disorder, biliary tract disorders, in a state of shock, in an altered state of consciousness for unknown reasons, with problems affecting the respiratory center or the respiratory function, or with an increased intracranial pressure.
- Symptoms of withdrawal reaction may occur even at therapeutic doses and for short term treatment. Withdrawal symptoms may be avoided by tapering it at the time of discontinuation especially after long treatment periods.
- Use of tramadol HCl during general anesthesia with enflurane and nitrous oxide may enhance intra-operative recall. Use of tramadol HCl during light planes of anesthesia should be avoided.

4.5 Interaction with other medicaments and other forms of interaction

- As medically appropriate, periodic evaluation of prothrombin time should be performed when tramadol HCl + paracetamol and warfarin like compounds are administered concurrently due to reports of increased INR.
- The pre- or postoperative application of the antiemetic 5-HT3 antagonist ondansetron increased the requirement of tramadol HCl in patients with postoperative pain.
- Drugs that inhibit CYP3A4 isozyme may inhibit the metabolism of tramadol HCl and probably M1.
- Busulfan is eliminated from the body via conjugation with glutathione. Concomitant use with paracetamol may result in reduced busulfan clearance.
- Concomitant diflunisal increases paracetamol plasma concentrations and this may increase hepatotoxicity.

4.6 Fertility, pregnancy and lactation

Pregnancy

Tramadol HCl + Paracetamol should not be used during pregnancy.

Nursing Mother
Tramadol HCl and its metabolites are found in small amounts in human breast milk. Therefore, Tramadol HCl + Paracetamol should not be used during breast feeding.

4.7 Effects on ability to drive and use machines

Tramadol HCl 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

Very Common:
Dizziness, somnolence & nausea.

Common:
Headache, trembling, confusion, mood changes (anxiety, nervousness, euphoria), sleep disorders, vomiting, constipation, dry mouth, diarrhea, abdominal pain, dyspepsia, flatulence, sweating & pruritus.

Uncommon:
Hypertension, palpitations, tachycardia, arrhythmia, involuntary muscular contractions, paraesthesia, tinnitus, depression, hallucinations, nightmares, amnesia, dyspnea, dysphagia, melaena, hepatic transaminases increase, dermal reactions (e.g.rash, urticaria), albuminuria, micturition disorders (dysuria and urinary retention), shivers, hot flushes & thoracic pain.

4.9 Overdose

Symptoms:
Symptoms on intoxication with tramadol HCl include in particular miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest. 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.

Treatment:

Supportive measures such as maintaining the patency of the airway and maintaining cardiovascular function should be instituted. In the treatment of paracetamol overdose, gastric decontamination with activated charcoal should be administered. Irrespective of the reported quantity of paracetamol ingested, the antidote for paracetamol, N-acetylcysteine, should be administered orally or intravenously, as quickly as possible, if possible, within 8 hours following the overdose.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Mechanism of Action

Tramadol HCl

Tramadol HCl is a pure non-selective agonist 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.

Paracetamol

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

5.2 Pharmacokinetic properties

Absorption

Tramadol HCl

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

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 HCl**.**

Effect of Food

The oral administration of tramadol HCl + paracetamol with food has no significant effect on the peak plasma concentration or extent of absorption of either tramadol HCl or paracetamol so that Traloget Plus can be taken independently of meal times.

Distribution

Tramadol HCl
Tramadol HCl has a high tissue affinity (Vd,ß=203 ± 40L). It has a plasma protein binding of about 20%.

Paracetamol
Paracetamol appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0.9L/kg. A relative small portion (~20%) of paracetamol is bound to plasma proteins.

Metabolism
Tramadol HCl
Tramadol HCl 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 HCl is metabolized 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.

Paracetamol
Paracetamol is principally metabolized in the liver through two major hepatic routes: glucuronidation and sulphation. 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.

Excretion
Tramadol HCl
Tramadol HCl and its metabolites are eliminated mainly by the kidneys.

Paracetamol
The half-life of paracetamol is approximately 2 to 3 hours in adults. 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core
Powdered Cellulose
Pregelatinized Starch
Corn Starch
Sodium Starch Glycolate
Magnesium Stearate
Purified Water

Coat (Opadry II Green 85G210002)
Purified Water
Purified Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

2 years. The expiration date refers to the product correctly stored in the required conditions.

6.4 Special precautions for storage

Do not store above 30 ^{0}C. Protect from sunlight & moisture.

6.5 Nature and contents of container

Traloget Plus (Tramadol HCl + Paracetamol) Tablets 37.5mg + 325mg is available in an Alu-Alu blister of 1 x 10's Tablets in a unit carton along with a package insert.

6.6 Instructions for use/handling

Keep out of reach of children.
To be sold on prescription of a registered medical practitioner only.

7. Marketing Authorisation Holder and Manufacturing Site Address

Marketing authorisation holder

Getz Pharma (Private) Limited
29-30/27, Korangi Industrial Area
Karachi 74900, Pakistan
Tel: (92-21) 5063100-03

Fax: (92-21) 5060141

Manufacturing Site Address

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29-30, Sector 27, Korangi Industrial Area,
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Website: www.getzpharma.com http://www.getzpharma.com/
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8. Marketing authorisation number(s)

H2024/CTD9730/21224

9. Date of first authorisation/renewal of the authorisation

Date of first authorization: 23-Feb-2024.

10. Date of revision of the text

Nov-2024