1.5.3 Patient information leaflet (PIL).*Refer to attached.*

Penoff ®

(Tramadol hydrochloride tablet).

Composition

Each Penoff tablet contains: Tramadol hydrochloride BP 50mg.

Pharmacology

Tramadol is a centrally acting synthetic analgesic compound. It is a non-selective pure agonist at mu, delta and kappa opioid receptors with a higher affinity for the mu receptor.

Tramadol and its O-desmethyl metabolite (M1) are selective, weak OP3-receptor agonists. Opiate receptors are coupled with G-protein receptors and function as both positive and negative regulators of synaptic transmission via G-proteins that activate effector proteins. As the effector system is adenylate cyclase and cAMP located at the inner surface of the plasma membrane, opioids decrease intracellular cAMP by inhibiting adenylate cyclase. Subsequently, the release of nociceptive neurotransmitters such as substance P, GABA, dopamine, acetylcholine and noradrenaline is inhibited. The analgesic properties of Tramadol can be attributed to norepinephrine and serotonin reuptake blockade in the CNS, which inhibits pain transmission in the spinal cord. The (+) enantiomer has higher affinity for the OP3 receptor and preferentially inhibits serotonin uptake and enhances serotonin release. The (-) enantiomer preferentially inhibits norepinephrine reuptake by stimulating alpha(2)-adrenergic receptors.

Pharmacokinetics

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-metabolized 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 t1/2,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 metabolized 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 t1/2,ß (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 + 4.9 h (tramadol) and 18.5 + 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 + 3.2 h and 16.9 + 3 h, in an extreme case 19.5 h and 43.2 h respectively.

Indications:

Penoff tablets are indicated for use in the treatment of moderate to severe pain. Its consider for those patients who are prone to constipation or respiratory depression. Tramadol is used to treat postoperative, dental, cancer, and acute musculoskeletal pain and as an adjuvant to NSAID therapy in patients with osteoarthritis.

Directions for use: For oral administration.

Dosage:

Acute pain: Adults and children over age 12 years: 50-100mg 3-4 times daily. Patients with low weight should use 0.7mg/kg bodyweight. Duration of therapy depends upon clinical need.

Chronic pain: An initial dose of 50mg or 100mg is followed by doses of 50mg or 100mg, every 4 to 6 hours, according to pain severity.

In elderly, 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

Patients with renal impairment/renal dialysis: For patients with creatinine clearance <30ml/min, the dosage interval should be increased to 12 hours.

Children under 12 years: Not recommended.

Contra-indications:

Hypersensitivity to the active substance or any of the other excipient, Acute intoxication with central nervous system depressants (alcohol, hypnotics, centrally acting analgesics, opioids, psychotropic drugs), in patients receiving monoamine oxidase inhibitors or within two weeks of their withdrawal

Severe hepatic impairment, severely impaired kidney function (creatinine clearance less than 10ml/min), severe respiratory impairment, Epilepsy not controlled by adequate treatment. It should not be administered during breastfeeding if long term treatment, i.e. more than 2 to 3 days, is necessary

• For use in narcotic withdrawal treatment.

Warning and precautions.

At therapeutic doses Tramadol has the potential to cause withdrawal symptoms.

• Drug dependence and abuse hence clinical need for 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 only be for short periods and under medical supervision.

• Opioid-dependent patients. Tramadol is not suitable as a substitute in these patients and cannot suppress morphine withdrawal symptoms.

• In patients sensitive to opiates the product should only be used with caution.

• Tramadol should be used with caution in patients with head injury, increased intracranial pressure, impairment of hepatic (metabolism of tramadol and active metabolite is reduced) and renal (decreased rate and extent of excretion of tramadol and the active metabolite) function, decreased level of consciousness and in patients prone to convulsive disorder or in shock.

• Patients prone to convulsive disorders. Convulsions have been reported at therapeutic doses and the risk may be increased at doses exceeding the usual upper daily dose limit. Patients with a history of epilepsy or those susceptible to seizures should only be treated with tramadol if there are compelling clinical reasons. The risk of convulsions may increase in patients taking tramadol and concomitant medication that lowers the seizure threshold (see Interactions with other medicaments and other forms of interactions section).

• 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.

• The concomitant use of carbamazepine or concomitant intake of alcohol with tramadol is not recommended

• Buprenorphine and other mixed agonists-antagonists, naltrexone.

Adverse reactions.

Most commonly reported adverse reactions are nausea and dizziness. Other includes vomiting, constipation, dry mouth, sweating and fatigue. Uncommon adverse reaction include

Cardiovascular regulation (palpitation, tachycardia, postural hypotension or cardiovascular collapse) and dermal reactions. Rare adverse reactions include Allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis. Symptoms of withdrawal reactions, similar to those occurring during opiate withdrawal, may occur as follows: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms. Other symptoms that are seen rarely with tramadol discontinuation include: panic attacks, severe anxiety, hallucinations, paraesthesias, tinnitus and unusual CNS symptoms.

Interaction with other medicinal products and other forms of interaction.

Tramadol 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.

Concomitant administration of Tramadol with other centrally depressant medicinal products including alcohol may potentiate the CNS effects. The results of pharmacokinetic studies have so far shown that on the concomitant or previous administration of cimetidine (enzyme inhibitor) clinically relevant interactions are unlikely to occur. Simultaneous or previous administration of carbamazepine (enzyme inducer) may reduce the analgesic effect and shorten the duration of action.The combination with mixed agonist/antagonists (e.g. buprenorphine, nalbuphine, pentazocine) and tramadol is not advisable, because the analgesic effect of a pure agonist may be theoretically reduced in such circumstances. Tramadol can induce convulsions and increase the potential for selective serotonin re-uptake inhibitors, (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic anti-depressants, anti-psychotics and other seizure threshold lowering medicinal products (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions.

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. Signs of serotonin syndrome may be for example confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus and diarrhoea. Serotonin syndrome is likely when there is: • Spontaneous clonus.• Inducible or ocular clonus with agitation or diaphoresis and Tremor and hyperreflexia

• Hypertonia and body temperature > 38 °C and inducible or ocular clonus.

Withdrawal of the serotoninergic medicinal products usually brings about a rapid improvement. Treatment depends on the nature and severity of the symptoms.

Caution should be exercised during concomitant treatment with tramadol and coumarin derivatives (e.g. warfarin) due to reports of increased INR with major bleeding and ecchymoses in some patients. 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.

Fertility, pregnancy and lactation

Animal studies with tramadol revealed at very high doses effects on organ development, ossification and neonatal mortality. Teratogenic effects were not observed. Tramadol crosses the placenta. There is inadequate evidence available on the safety of tramadol in human pregnancy. Therefore tramadol should not be used in pregnant women. Tramadol is not recommended during breast-feeding. After a single administration of tramadol it is not usually necessary to interrupt breast-feeding.

Effects on driving and use of machine:

Tramadol may cause effects such as somnolence and dizziness and therefore may impair the reactions of drivers and machine operators. Do not drive or operate machines.

Overdose:

Symptoms of overdosage are typical of other opioid analgesics and include miosis, vomiting, cardiovascular collapse, sedation and coma, seizures and respiratory depression. 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 by haemodialysis and haemofiltration. Therefore treatment of acute intoxication with tramadol by haemodialysis or haemofiltration is not recommended.

Presentation:

Tablet: Blister packs of 2 x10 are in a unit box.

Storage

Store below 30^0C, Protect from light and moisture.

Keep all medicines out of reach of children.

Manufactured by:

DAWA	**DAWA Limited,** **Plot No. 7879/8, Baba Dogo Road, Ruaraka** **P. O. Box 16633 – 00620, Nairobi, Kenya.**

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1.5.4. Mock-ups and specimens. *Not applicable.*