For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

DOMADOL PLUS

1. Generic Name

Acetaminophen & Tramadol Hydrochloride Tablets U.S.P.

2. Qualitative and quantitative composition

Each film coated tablet contains:

Tramadol Hydrochloride I.P. …..37.5 mg

Paracetamol I.P. ……....325 mg

Excipients……q.s.

Colour: Yellow Oxide of Iron USPNF

The excipients used are Starch, Microcrystalline Cellulose, Sodium Starch Glycolate, Povidone K-30, Colloidal Silicon Dioxide, Talc, Magnesium Stearate, Opadry 03B82982 Yellow, Isopropyl Alcohol and Dichloromethane.

3. Dosage form and strength

Dosage form: Film Coated Tablets

Strength: Tramadol - 37.5 mg and Paracetamol - 325 mg

4. Clinical particulars

4.1 Therapeutic indication

It is indicated for short term (five days or less) management of acute pain in adults.

4.2 Posology and Method of Administration

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 adjusted to intensity of pain and the sensitivity of the individual patient. The lowest effective dose for analgesia should generally be selected. The total dose of 8 tablets (equivalent to 300 mg tramadol hydrochloride and 2600 mg paracetamol) per day should not be exceeded. The dosing interval should not be less than six hours.

Adults and adolescents (12 years and older)

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 (see also section 4.4 - Special warnings and precautions for use). 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.

Paediatric population

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.

Older patients

A dose adjustment is not usually necessary in patients up to 75 years without clinically manifest hepatic or renal insufficiency. In older people over 75 years' elimination may be prolonged. Therefore, if necessary the dosage interval is to be extended according to the patient's requirements.

Renal insufficiency / dialysis

In patients with renal insufficiency the elimination of tramadol is delayed. In these patient's prolongation of the dosage intervals should be carefully considered according to the patient's requirements.

Hepatic impairment

In patients with hepatic impairment the elimination of tramadol is delayed. In these patient's prolongation of the dosage intervals should be carefully considered according to the patient's requirements. Because of the presence of paracetamol Tramadol hydrochloride/Paracetamol should not be used in patients with severe hepatic impairment.

Method of administration

Oral use

Tablets must be swallowed whole, with a sufficient quantity of liquid. They must not be broken or chewed.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients,

- 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

- severe hepatic impairment,

- epilepsy not controlled by treatment

4.4 Special warnings and precautions for use

Warnings:

- In adults and adolescents 12 years and older. The maximum dose of 8 tablets of Tramadol hydrochloride/Paracetamol should not be exceeded. 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 insufficiency (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 insufficiency, 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.

- Convulsions have been reported in tramadol-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 anaesthesia. Epileptic patients controlled by a treatment or patients susceptible to seizures should be treated with this medicine only if there are compelling circumstances. Convulsions have been reported in patients receiving tramadol at the recommended dose levels. The risk may be increased when doses of tramadol exceed the recommended upper dose limit

- Concomitant use of opioid agonists-antagonists (nalbuphine, buprenorphine, etazocine) is not recommended

Precautions for use

Tolerance and physical and/or psychological dependence may develop, even at therapeutic doses. The clinical need for analgesic treatment should be reviewed regularly (see section 4.2). 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 hydrochloride/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.

Paracetamol in overdosage may cause hepatic toxicity in some patients.

Symptoms of withdrawal reaction, similar to those occurring during opiate withdrawal, 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. Rarely, cases of dependence and abuse have been reported.

- In one study, use of tramadol during general anaesthesia with enflurane and nitrous oxide was reported to enhance intra-operative recall. Until further information is available, use of tramadol during light planes of anaesthesia should be avoided.

Tramadol hydrochloride/Paracetamol tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Drugs interactions

Concomitant use is contraindicated with:

• Non-selective MAO Inhibitors

Risk of serotonergic syndrome: diarrhoea, tachycardia, hyperhidrosis, trembling, confusional state, even coma.

• Selective-A MAO Inhibitors

Extrapolation from non-selective MAO inhibitors

Risk of serotonergic syndrome: diarrhoea, tachycardia, hyperhidrosis, trembling, confusional state, even coma.

• Selective-B MAO Inhibitors

Central excitation symptoms evocative of a serotonergic syndrome: diarrhoea, tachycardia, hyperhidrosis, trembling, confusional state, even coma.

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

Concomitant use is not recommended with:

• Alcohol

Alcohol increases the sedative effect of opioid analgesics.

The effect on alertness can make driving of vehicles and the use of machines dangerous.

Avoid intake of alcoholic drinks and of medicinal products containing alcohol.

• Carbamazepine and other enzyme inducers

Risk of reduced efficacy and shorter duration due to decreased plasma concentrations of tramadol.

• Opioid agonists-antagonists (buprenorphine, nalbuphine, pentazocine)

Decrease of the analgesic effect by competitive blocking effect at the receptors, with the risk of occurrence of withdrawal syndrome.

Concomitant use which needs to be taken into consideration:

• Tramadol can induce convulsions and increase the potential for selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, antipsychotics and 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 re-uptake inhibitors (SSRIs) serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors, tricyclic antidepressants and mirtazapine may cause serotonin toxicity.

• Serotonin Syndrome is likely when one of the following is observed:

- Spontaneous clonus
- Inducible or ocular clonus with agitation or diaphoresis,
- Tremor and hyperreflexia
- Hypertonia and body temperature > 38 °C and inducible or ocular clonus.

Withdrawal of the serotonergic drugs usually brings about a rapid improvement. Treatment depends on the type and severity of the symptoms.

• Other opioid derivatives (including antitussive drugs and substitutive treatments), benzodiazepines and barbiturates

Increased risk of respiratory depression which can be fatal in cases of overdose.

• Other central nervous system depressants, such as other opioid derivatives (including antitussive drugs and substitutive treatments), barbiturates, benzodiazepines, other anxiolytics,

hypnotics, sedative antidepressants, sedative antihistamines, neuroleptics, centrally-acting antihypertensive drugs, thalidomide and baclofen.

These drugs can cause increased central depression. The effect on alertness can make driving of vehicles and the use of machines dangerous.

• As medically appropriate, periodic evaluation of prothrombin time should be performed when Tramadol hydrochloride/Paracetamol and warfarin like compounds are administered concurrently due to reports of increased INR.

• In a limited number of studies the pre- or postoperative application of the antiemetic 5-HT3 antagonist ondansetron increased the requirement of tramadol in patients with postoperative pain.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

Since this medicine is a fixed combination of active ingredients including tramadol, it should not be used during pregnancy.

• Data regarding paracetamol:

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosages.

• Data regarding tramadol:

Tramadol should not be used during pregnancy as there is inadequate evidence available to assess the safety of tramadol in pregnant women. Tramadol administered before or during birth does not affect uterine contractility. In neonates it may induce changes in the respiratory rate which are usually not clinically relevant. Long-term treatment during pregnancy may lead to withdrawal symptoms in the newborn after birth, as a consequence of habituation.

Breast-feeding:

Since this medicine is a fixed combination of active ingredients including tramadol, it should not be ingested during breast feeding.

• Data regarding paracetamol:

Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast feeding by women using single ingredient medicinal products containing only paracetamol.

• Data regarding tramadol:

Approximately 0.1% of the maternal dose of tramadol is excreted in breast milk. In the immediate post-partum period, for maternal oral daily dosage up to 400 mg, this corresponds to a mean amount of tramadol ingested by breast-fed infants of 3% of the maternal weight-adjusted dosage. For this reason, tramadol should not be used during lactation or alternatively, breast-feeding should be discontinued during treatment with tramadol. Discontinuation of breast-feeding is generally not necessary following a single dose of tramadol.

Fertility

Post marketing surveillance does not suggest an effect of tramadol on fertility.

Animal studies did not show an effect of tramadol on fertility. No study on fertility was accomplished with the combination of tramadol and paracetamol.

4.7 Effects on ability to drive and use machines

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.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

• The medicine is likely to affect your ability to drive

• Do not drive until you know how the medicine affects you

• It is an offence to drive while under the influence of this medicine

• However, you would not be committing an offence (called 'statutory defence') if:

- The medicine has been prescribed to treat a medical or dental problem and
- You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
- It was not affecting your ability to drive safely

4.8 Undesirable effects

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

The frequencies are defined as follows:

Very common:	≥1/10
Common:	≥1/100 to <1/10
Uncommon:	≥1/1000 to <1/100
Rare:	≥1/10 000 to <1/1000
Very rare:	<1/10 000
Unknown:	Frequency cannot be estimated from the available data

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Cardiac disorders:

• Uncommon: palpitations, tachycardia, arrhythmia.

Eye disorders:

• Rare: vision blurred, miosis, mydriasis

Ear and labyrinth disorders:

• Uncommon: tinnitus

Gastro-intestinal disorders:

• Very common: nausea

• Common: vomiting, constipation, dry mouth, diarrhoea abdominal pain, dyspepsia, flatulence

• Uncommon: dysphagia, melaena

General disorders and administration site conditions:

• Uncommon: chills, chest pain

Investigations:

• Uncommon: transaminases increased

Metabolism and nutrition disorders:

• Unknown: hypoglycaemia

Nervous system disorders:

• Very common: dizziness, somnolence

• Common: headache trembling

• Uncommon: involuntary muscular contractions, paraesthesia, amnesia

• Rare: ataxia, convulsions, syncope, speech disorders.

Psychiatric disorders:

• Common: confusional state, mood altered, anxiety, nervousness, euphoric mood), sleep disorders

• Uncommon: depression, hallucinations, nightmares

• Rare: delirium, drug dependence.

Post marketing surveillance

very rare: abuse.

Renal and urinary disorders:

• Uncommon: albuminuria, micturition disorders (dysuria and urinary retention)

Respiratory, thoracic and mediastinal disorders:

• Uncommon: dyspnoea

Unknown : Hiccups

Skin and subcutaneous tissue disorders:

• Common: hyperhidrosis, pruritus

• Uncommon: dermal reactions (e.g. Rash, urticaria).

Vascular disorders:

• Uncommon: hypertension, hot flush

Although not observed during clinical trials, the occurrence of the following undesirable effects known to be related to the administration of tramadol or paracetamol cannot be excluded:

Tramadol

• Postural hypotension, bradycardia, collapse (tramadol).

• Post-marketing surveillance of tramadol has revealed rare alterations of warfarin effect, including elevation of prothrombin times.

• Rare cases (≥ 1/10000 to < 1/1000): allergic reactions with respiratory symptoms (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis

• Rare cases (≥ 1/10000 to < 1/1000): changes in appetite, motor weakness, and respiratory depression

• Psychic side-effects may occur following administration of tramadol which vary individually in intensity and nature (depending on personality and duration of medication). These include changes in mood, (usually euphoric mood occasionally dysphoria), changes in activity (usually suppression occasionally increase) and changes in cognitive and sensorial capacity (e.g. decision behaviour perception disorders).

• Worsening of asthma has been reported though a causal relationship has not been established.

• Symptoms of drug withdrawal syndrome, similar to those occurring during opiate withdrawal may occur as follows: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms. Other symptoms that have very rarely been seen if tramadol hydrochloride is discontinued abruptly include: panic attacks, severe anxiety, hallucinations, paraesthesia, tinnitus and unusual CNS symptoms.

Paracetamol

• Adverse effects of paracetamol are rare but hypersensitivity including skin rash may occur. There have been reports of blood dyscrasias including thrombocytopenia and agranulocytosis, but these were not necessarily causally related to paracetamol.

• There have been several reports that suggest that paracetamol may produce hypoprothrombinaemia when administered with warfarin-like compounds. In other studies, prothrombin time did not change.

• Very rare cases of serious skin reactions have been reported.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

https://torrentpharma.com/index.php/site/info/adverse_event_reporting.

4.9 Overdose

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 encephalopathy, 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.

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention and any adult or adolescent who had ingested around 7.5 g or more of paracetamol in the preceding 4 hours or any child who has ingested ≥150 mg/kg of paracetamol in the preceding 4 hours should undergo gastric lavage. Paracetamol concentrations in blood should be measured later than 4 hours after overdose in order to be able to assess the risk of developing liver damage (via the paracetamol overdose nomogram). Administration of oral methionine or intravenous N-acetylcysteine (NAC) which may have a beneficial effect up to at least 48 hours after the overdose, may be required. Administration of intravenous NAC is most beneficial when initiated within 8 hours of overdose ingestion. However, NAC should still be given if the time to presentation is greater than 8 hours after overdose and continued for a full course of therapy. NAC treatment should be started immediately when massive overdose is suspected. General supportive measures must be available.

Irrespective of the reported quantity of paracetamol ingested, the antidote for paracetamol, NAC, should be administered orally or intravenously, as quickly as possible, if possible, within 8 hours following the overdose.

5. Pharmacological properties

5.1 Mechanism of Action

Paracetamol

Paracetamol is an antipyretic analgesic. The mechanism of action is probably similar to that of aspirin and dependant on the inhibition of prostaglandin synthesis. This inhibition appears however to be on a selective basis.

Tramadol

Tramadol is an opioid analgesic that acts on the central nervous system. Tramadol is a 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.

5.2 Pharmacodynamic properties

Pharmacotherapeutic group: Opioids in combination with non-opioid analgesics; tramadol and paracetamol.

ATC code: N02A J 13

ANALGESICS

Tramadol is an opioid analgesic that acts on the central nervous system. Tramadol 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. 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

5.3 **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 is 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 P 450 to an active intermediate (the N-acetyl benzoquinone mine) 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.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

No preclinical study has been performed with the fixed combination (tramadol and paracetamol) to evaluate its carcinogenic or mutagenic effects or its effects on fertility.

No teratogenic effect that can be attributed to the medicine has been observed in the progeny of rats treated orally with the combination tramadol/paracetamol.

The combination tramadol/paracetamol has proven to be embryotoxic and foetotoxic in the rat at materno-toxic dose (50/434 mg/kg tramadol/paracetamol), i.e., 8.3 times the maximum therapeutic dose in man. No teratogenic effect has been observed at this dose. The toxicity to the embryo and the foetus results in a decreased foetal weight and an increase in supernumerary ribs. Lower doses, causing less severe materno-toxic effect (10/87 and 25/217 mg/kg tramadol/paracetamol) did not result in toxic effects in the embryo or the foetus.

Results of standard mutagenicity tests did not reveal a potential genotoxic risk for tramadol in man.

Results of carcinogenicity tests do not suggest a potential risk of tramadol for man.

Animal studies with tramadol revealed, at very high doses, effects on organ development, ossification and neonatal mortality, associated with maternotoxicity. Fertility reproductive performance and development of offspring were unaffected. Tramadol crosses the placenta. Male and female fertility was not affected.

Extensive investigations showed no evidence of a relevant genotoxic risk of paracetamol at therapeutic (i.e. non-toxic) doses.

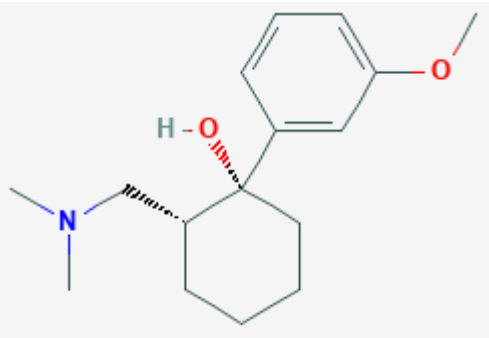
Long-term studies in rats and mice yielded no evidence of relevant tumorigenic effects at non-hepatotoxic dosages of paracetamol.

Animal studies and extensive human experience to date yield no evidence of reproductive toxicity.

7. Description

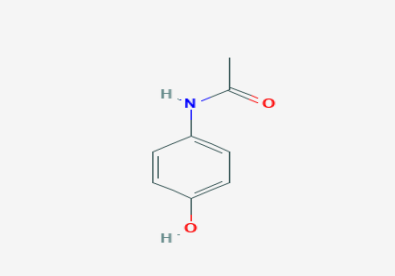
Tramadol

Tramadol is chemically (1*R*,2*R*)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexan-1-ol having molecular formula of $C_{16}H_{25}NO_2$ and molecular weight is 263.37 and chemical structure is:



Paracetamol

Paracetamol is 4-hydroxyacetanilide having molecular formula of $C_8H_9NO_2$ and molecular weight is 151.2 and the chemical structure is:



Paracetamol is white crystals or white, crystalline powder which is freely soluble in ethanol (95%) and in acetone; sparingly soluble in water; very slightly soluble in dichloromethane and in ether.

Acetaminophen & Tramadol Hydrochloride Tablets are yellow coloured, capsule shaped, biconvex, film coated tablet plain on one side and breakline on the other side. The excipients used are Starch, Microcrystalline Cellulose, Sodium Starch Glycolate, Povidone K-30, Colloidal Silicon Dioxide, Talc, Magnesium Stearate, Opadry 03B82982 Yellow, Isopropyl Alcohol and Dichloromethane.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable.

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

DOMADOL PLUS is available in blister pack of 10 tablets.

8.4 Storage and handing instructions

Store in a cool, dry place. Protect from light.

Keep all medicines out of reach of children.

9. Patient Counselling Information

DOMADOL PLUS

37.5mg/325mg film-coated tablets Tramadol hydrochloride/Paracetamol

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

· Keep this leaflet. You may need to read it again.

· If you have any further questions, ask your doctor or pharmacist.

· This medicine has been prescribed for you only. Do not pass it on to others; it may harm them, even if their signs of illness are the same as yours.

· If you get any side effects, talk to your doctor or pharmacist. This includes any possible side Effects not listed in this leaflet.

What is in this leaflet?

9.1. What DOMADOL PLUS is and what it is used for

9.2. What you need to know before you take DOMADOL PLUS

9.3. How to take DOMADOL PLUS

9.4. Possible side effects

9.5. How to Store DOMADOL PLUS

9.6. Contents of the pack and other information

9.1 DOMADOL PLUS is and what it is used for
DOMADOL PLUS is combination of Tramadol and Paracetamol

DOMADOL PLUS is used to treat moderate to severe pain when your doctor recommends that a combination of tramadol hydrochloride and paracetamol is needed.

9.2 What you need to know before you take DOMADOL PLUS
Do not take DOMADOL PLUS

- If you are allergic to tramadol hydrochloride, paracetamol or any of the other ingredients of this medicine
- In cases of acute alcohol poisoning
- If you are taking sleeping pills, pain relievers or medicines that affect mood and emotions
- If you are also taking medicines called monoamine oxidase inhibitors (MAOIs) or have taken MAOIs in the last 14 days before treatment with DOMADOL PLUS. MAOIs are used in the treatment of depression or Parkinson's disease.• if you have a severe liver disorder
- If you have epilepsy that is not adequately controlled by your current medicine.

Warnings and precautions

Talk to your doctor before taking DOMADOL PLUS

- If you take other medicines containing paracetamol or tramadol
- If you have liver problems or disease as your eyes and skin may turn yellow, which may suggest jaundice
- If you have kidney problems \
- If you have severe difficulties in breathing, for example asthma or severe lung problems
- If you have epilepsy or have already experienced fits or seizures
- If you have recently suffered from a head injury, shock or severe headaches associated with vomiting (being sick)
- If you are dependent on any medicine (for example morphine)
- If you take other medicines to treat pain that contain buprenorphine, nalbuphine or pentazocine
- If you are going to have an anaesthetic (tell your doctor or dentist that you are taking DOMADOL PLUS). If any of the above-mentioned points applied to you in the past or applies to you while you are taking DOMADOL PLUS, please make sure your doctor knows. He/she can then decide whether you should continue to use this medicine.

Other medicines and DOMADOL PLUS

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Do not exceed the maximum daily doses of paracetamol or tramadol from this or

other medicines. Do not take DOMADOL PLUS with MAOIs (see section 'Do not take DOMADOL PLUS'). DOMADOL PLUS is not recommended to be taken with the following:

- Carbamazepine (a medicine used to treat epilepsy or some types of pain)
- Buprenorphine, nalbuphine or pentazocine (opioid-type pain relievers). The risk of side effects increases
- If you are taking triptans (used for migraine) or selective serotonin re-uptake inhibitors (SSRIs, used for depression). Check with your doctor if you experience confusion, restlessness, fever, sweating, uncoordinated movement of limbs or eyes, uncontrollable jerking of muscles or diarrhoea.
- If you are taking tranquilizers, sleeping pills, other pain relievers such as morphine and codeine (also as cough medicine), baclofen (a muscle relaxant), medicines used to lower blood pressure, or medicines to treat allergies. Check with your doctor if you feel drowsy or feel faint.
- If you are taking medicines which may cause convulsions (fits), such as certain antidepressants or antipsychotics. The risk having a fit may increase if you take DOMADOL PLUS at the same time. Your doctor will tell you whether DOMADOL PLUS is suitable for you.
- If you are taking warfarin or phenprocoumon (for blood thinning). The effectiveness of such medicines may be altered and bleeding may occur (see section 4). The effectiveness of DOMADOL PLUS may be altered if you also take:
- Metoclopramide, domperidone or ondansetron (medicines used to treat nausea and vomiting/being sick)
- Cholestyramine (medicine used to reduce cholesterol in the blood)
- If you are taking certain antidepressants. DOMADOL PLUS may interact with these medicines and you may experience symptoms such as involuntary, rhythmic contractions of muscles, including the muscles that control movement of the eye, agitation, excessive sweating, tremor, exaggeration of reflexes, increased muscle tension, body temperature above 38 °C.

DOMADOL PLUS with food and alcohol

Do not drink alcohol while you are taking DOMADOL PLUS, as you may feel drowsier.

Pregnancy, breast-feeding and fertility

Do not take DOMADOL PLUS while you are pregnant or breast-feeding. Check with your doctor if you become pregnant during treatment with DOMADOL PLUS and before taking any further tablets. Tramadol is excreted into breast milk. For this reason, you should not take DOMADOL PLUS more than once during breast-feeding, or alternatively, if you take DOMADOL PLUS more than once, you should stop breast-feeding. Based on human experience tramadol is suggested not to influence female or male fertility. No data on the influence of the combination of DOMADOL PLUS on fertility are available. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

If you feel drowsy while taking DOMADOL PLUS, do not drive, use tools or use machinery.

The medicine can affect your ability to drive as it may make you sleepy or dizzy.

- Do not drive while taking this medicine until you know how it affects you.
- It is an offence to drive if this medicine affects your ability to drive.

• However, you would not be committing an offence if:

- The medicine has been prescribed to treat a medical or dental problem and

- You have taken it according to the instructions given by the prescriber or in the information provided with the medicine and

- It was not affecting your ability to drive safely

Talk to your doctor or pharmacist if you are not sure whether it is safe for you to drive while taking this medicine.

9.3 How to take DOMADOL PLUS

Always take this medicine exactly as you doctor has told you. Check with your doctor or Pharmacist if you are not sure.

The dosage should be adjusted to the intensity of your pain and your individual pain sensitivity. **In general the lowest pain-relieving dose should be taken.**

Take DOMADOL PLUS for as short a time as possible as and no longer than your doctor has told you.

Adults and adolescents over 12 years:

The recommended starting dose unless otherwise prescribed by your doctor is 2 tablets for adults and adolescents over 12 years. If required, further doses may be taken, as instructed by your doctor.

The shortest time between doses must be at least 6 hours.

Do not take more than 8 tablets per day.

Children under 12 years of age:

 not recommended.

Older people:

In elderly patients (above 75 years) the excretion of tramadol may be delayed. If this applies to **you, your doctor may recommend prolonging the dosage interval.**

Severe liver or kidney disease (insufficiency)/dialysis patients:

Patients with severe liver and/or kidney insufficiency should not take DOMADOL PLUS. If in your case the insufficiency is mild or moderate, your doctor may recommend prolonging the dosage interval.

Method of administration:

The tablets are for oral use.

Swallow the tablets whole with sufficient liquid**.**

Do not break or chew the tablets.

If you think that the effect of DOMADOL PLUS is too strong (you feel very drowsy or have difficulty breathing) or too weak (you do not have enough pain relief), contact your doctor.

If you take more DOMADOL PLUS than you should

Talk to a doctor at once if you take too much of this medicine even if you feel well. This is because too much paracetamol can cause delayed, serious liver damage**.**

If you forget to take DOMADOL PLUS

If you forget to take the tablets, pain is likely to return.

Do not take a double dose to make up for forgotten individual doses; simply continue taking the tablets as before.

If you stop taking DOMADOL PLUS

Generally, there will be no after-effects when treatment with DOMADOL PLUS is stopped. Rarely, people who have been using a medicine containing tramadol may become dependent on it, making it hard to stop taking it. If you have been taking DOMADOL PLUS for some time and want to stop, contact your doctor because your body may have become used to DOMADOL PLUS.

People may:

- feel agitated, anxious, nervous or shaky
- be over active
- have difficulty sleeping
- Have stomach or bowel disorders.

Very few people may also get:

- Panic attacks
- Hallucinations, unusual perceptions such as itching, tingling and numbness
- Ringing in the ears.

If you experience any of these complaints after stopping this medicine, please contact your doctor. Other side effect information is listed in section 4.

9.4 **Possible side effects**

Like all medicines, this medicine can cause side effects, however not everybody gets them.

Some side effects could be serious. Contact your doctor immediately if any of the following occur:

- Rarely cases of skin rash, indicating an allergic reaction, may develop with sudden swelling of the face and neck, difficulties breathing or drop of blood pressure and fainting. If this happens to you, stop treatment. Do not take the medicine again.
- Prolonged or unexpected bleeding, from the use of TRAMACET with medicines used to thin the blood (e.g. warfarin, phenprocoumon).

Additionally, if any of the following side effects get serious, contact your doctor or pharmacist:

Very common: may affect more than 1 in 10 people

- Nausea
- Dizziness, drowsiness.

Common: may affect up to 1 in 10 people

- vomiting (being sick), digestion problems (constipation, flatulence, and diarrhoea), stomach pain, dry mouth
- itching, sweating (hyperhidrosis)
- Headache, shaking

- Confusional state, sleep disorders, mood changes (anxiety, nervousness, and feeling of high spirits).

Uncommon: may affect up to 1 in 100 people 6

- increase in pulse or blood pressure, heart rate or heart rhythm disorders
- Tingling, numbness or feeling of pins and needles in the limbs, ringing in the ears, involuntary muscle twitching
- Depression, nightmares, hallucinations (hearing, seeing or sensing things that are not really there), memory lapses
- Difficulty breathing
- Difficulty swallowing, blood in the stools
- Skin reactions (for example rashes, hives)
- Increase in liver enzyme values
- Presence of albumin in urine, difficulties or pain on passing urine
- Shivering, hot flushes, pain in the chest

Rare: may affect up to 1 in 1,000 people

- fits, uncoordinated movements, transient loss of consciousness (syncope)
- Drug dependence
- Delirium
- Vision blurred, constriction of the pupil (miosis)
- Speech disorders
- Excessive dilation of the pupils (mydriasis)

Unknown: frequency unknown:

- Decrease in blood sugar level (hypoglycaemia)

In addition, the following side effects have been reported by people using medicines that contain only tramadol or only paracetamol:

- feeling faint when getting up from a lying or sitting position, slow heart rate, fainting
- Changes in appetite
- Muscle weakness, slower or weaker breathing
- Mood changes, changes in activity, changes in perception
- worsening of existing asthma
- Nose bleeds or bleeding gums, which may result from a low blood platelet count.
- Very rare cases of serious skin reactions have been reported with paracetamol.
- Rare cases of respiratory depression have been reported with tramadol.

Not Known

- Hiccups

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: https://torrentpharma.com/index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store DOMADOL PLUS

Store in a cool, dry place. Protect from light.

Keep all medicines out of reach of children.

9.6 Contents of the pack and other information

Each film coated tablet contains:

Tramadol Hydrochloride I.P. 37.5 mg and Paracetamol I.P 325 mg

The excipients used are Starch, Microcrystalline Cellulose, Sodium Starch Glycolate, Povidone K-30, Colloidal Silicon Dioxide, Talc, Magnesium Stearate, Opadry 03B82982 Yellow, Isopropyl Alcohol and Dichloromethane.

10. Details of manufacturer

Manufactured by:

Torrent Pharmaceuticals Ltd.

32 No. Middle Camp, NH-10, East District, Gangtok. Sikkim-737 135.

11. Details of permission or licence number with date

Mfg Licence No.: M/563/2010 issued on 24.07.2018

12. Date of revision

Not Applicable

MARKETED BY

torrent PHARMA

TORRENT PHARMACEUTICALS LTD.

IN/ DOMADOL PLUS 37.5 mg and 325 mg /may-20/01/PI