Symol Plus

(Tramadol HCl+Paracetamol) Tablets USP

37.5mg+325mg

سائمول پلس

(ٹراماڈول ہائیڈروکلورائیڈ+پیراسیٹامول) ٹیبلیٹس یو ایس پی

COMPOSITION
Each film coated tablet contains:
Tramadol Hydrochloride USP……..37.5mg.
Paracetamol USP……..325mg.
Finished product specs: USP

DESCRIPTION
Tramadol HCl/paracetamol 37.5 mg/325 is an orally administered fixed-dose combination of the atypical opioid tramadol and paracetamol, which is indicated for the symptomatic treatment of moderate to severe pain. Tramadol Hydrochloride is in a class of medications called opiate (narcotic) analgesics and is chemically described as (1R,2R)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexan--ol;hydrochloride. Its molecular formula is $C_{16}H_{26}CINO_2$ Paracetamol is an antipyretic and analgesic drug and is chemically described as N-(4 hydroxyphenyl) acetamide. The molecular formula is $C_8H_9NO_2$.

PHARMACOLOGY
Mechanism of Action
Tramadol is a centrally acting synthetic analgesic compound whose analgesic profile can be attributed to the binding of parent and 0-demethylated (M1) metabolite to μ-opioid receptors as well as the weak inhibition of neuronal re-uptake of noradrenaline and serotonin. Paracetamol also has centrally acting analgesic effects.

Tramadol is well attributed after oral administration, reaching peak activity in 2 to 3 hours. Oral absorption of paracetamol following co-administration of tramadol and Paracetamol gives a peak plasma concentration of paracetamol within 1 hour and is not affected by co-administration with tramadol. Tramadol and paracetamol are both extensively metabolized in the liver. Approximately 30% of tramadol is excreted unchanged in the urine. Tramadol and its metabolites are eliminated primarily by the kidney. The plasma elimination half-lives of tramadol and its M1 metabolite are approximately 6 and 7 hours respectively. Paracetamol is eliminated from the body primarily by formation of glucuronide and sulfate conjugates in a dose-dependent manner. The half-life of paracetamol is about 2-3 hours in adults. Less than 9% of paracetamol is excreted unchanged in the urine.

DOSAGE AND ADMINISTRATION
To be used in adults and children over 16 years of age. Do not exceed the recommended dose.

THERAPEUTIC INDICATIONS
Symol Plus tablets are indicated for the short term (Less than 5 days) management of acute pain.
Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve Symol Plus tablets for use in patients for whom alternative treatment options [e.g., non-opioid analgesics]:
- Have not been tolerated, or are not expected to be tolerated.
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia

CONTRAINDICATIONS
- Hypersensitivity to tramadol or paracetamol.
- Significant respiratory depression, acute or severe bronchial asthma (in unmonitored setting or lack of resuscitative equipment)
- Known or suspected gastrointestinal obstruction, including paralytic ileus; uncontrolled epilepsy.
- Acute intoxication with centrally-acting analgesics, opioids, hypnotics, psychotropic drugs, or alcohol.
- CYP2D6 ultrarapid and poor metabolizers.
- Severe hepatic impairment.
- Children <12 years; post-operative use in children <18 years who have undergone tonsillectomy and/or adenoidectomy; adolescents between 12-18 years who have other risk factors (e.g. obesity, obstructive sleep apnoea) that may increase their sensitivity to respiratory depression.
- Concomitant use or within 2 weeks after MAOI therapy.

SIDE EFFECTS
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, difficulty in 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 tramadol hydrochloride/paracetamol tablets 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 side effects (affecting more than 1 in 10 people treated)
- Nausea.
- Dizziness, drowsiness.

Common side effects (affecting less than 1 in 10, but more than 1 in 100 people treated)
- Vomiting (being sick), digestion problems (constipation, flatulence, diarrhoea), stomach pain, dry mouth.
- Itching, sweating.
- Headache, shaking.
- Confusion, sleep disorders, mood changes (anxiety, nervousness, feeling of high spirits).

Uncommon side effects (affecting less than 1 in 100, but more than 1 in 1,000 people treated).
- Increase in pulse or blood pressure, heart rate or heart rhythm disorders.
- Difficulty or pain on passing water.
- Skin reactions (for example rashes, hives).
- 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 swallowing, blood in the stools.
- Shivering, hot flushes, pain in the chest.
- Difficulty breathing.

Rare side effects (affecting less than 1 in 1,000, but more than 1 in 10,000 people treated).
- Fits, uncoordinated movements.
- Addiction.
- Blurred vision.
- Transient loss of consciousness (syncope).
- Unknown frequency.
- Decrease in blood sugar level.

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.

WARNINGS AND PRECAUTIONS
Dosages in excess of those recommended may cause severe liver damage. Patients suffering from liver or kidney disease should take paracetamol containing products under medical supervision.

Seizures
Seizures have been reported in patients receiving tramadol at dosages within the recommended dosage range. The risk of seizures is enhanced in patients exceeding the recommended dose, or in patients taking tricyclic anti-depressants or other tricyclic compounds e.g. promethazine, selective serotonin re-uptake inhibitors, MAO-inhibitors and neuroleptics.

Skin Reactions
Rarely, acetaminophen (paracetamol) may cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Patients should be informed about the signs of serious skin reactions, and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Drug Abuse and Dependence
Although tramadol has a low dependence potential, tolerance, psychic and physical dependence of the morphine-type (μ-Opioid) may develop with long-term use.

Effects on Ability to Drive or Operate Machinery
Tramadol may affect reactions to the extent that driving ability and the ability to operate machinery may be impaired. This applies particularly in conjunction with other psychotropic medicines including alcohol.

PRECAUTIONS

Children	Elderly	Pregnancy	Lactation
Safety and Efficacy have not been established	Use with caution, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease and multiple drug therapy.	Pregnancy category C drug.	Since this medicine is a fixed combination of active ingredients including tramadol, it should not be ingested during breast feeding. Administration to nursing women is not recommended as tramadol may be secreted in breast milk and may cause respiratory depression in the infant.

DRUG INTERACTIONS
Concomitant use is contraindicated with:
Non-selective MAO inhibitors
Risk of serotonergic syndrome: diarrhoea, tachycardia,

hyperhidrosis, trembling, confusion, and coma.

Selective-A MAO inhibitors
- Extrapolation from non-selective MAO inhibitors.
- Risk of serotonergic syndrome: diarrhoea, tachycardia, hyperhidrosis, trembling, confusion, and coma.

Selective-B MAO inhibitors
- Central excitation symptoms evocative of a serotonergic syndrome: diarrhoea, tachycardia, hyperhidrosis, trembling, confusion, and 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 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 syndrome, a potentially life-threatening condition.
- Other opioid derivatives (including antitussive drugs and substitutive treatments) 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), 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.
- Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risks factors.

Sedating medicinal products such as benzodiazepines or related substances:
- The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited.
- As medically appropriate, periodic evaluation of prothrombin time should be performed when Tramadol/Paracetamol and warfarin like compounds are administered concurrently due to the reports of increased INR.
- In a limited number of studies, the pre- or post-operative application of the antiemetic 5HT3-antagonist, ondansetron, increased the requirement for tramadol in patients with post-operative pain.

OVERDOSAGE
Tramadol/Paracetamol is a fixed combination of active substances. In case of overdose, the symptoms may include the signs and symptoms of toxicity of tramadol and/or paracetamol or of both these active ingredients. Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

Symptoms of an 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 including coma, convulsions and respiratory depression, including respiratory arrest. Serotonin syndrome has also been reported.

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 arrhythmia 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 excessive quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested) become irreversibly bound to liver tissue.

STORAGE CONDITIONS
- Protect from heat, light and moisture.
- Store below 30°C.

PRESENTATION
Symol Plus (Tramadol HCl + Paracetamol) tablets 37.5mg+325mg is available as packs of 10 tablets.

To be sold on prescription of a registered medical practitioner only.

Keep all medicines out of reach of children.

Manufactured by :
Indus Pharma (Pvt.) Ltd.
65/27, Korangi Industrial Area,
Karachi-74900, Pakistan.

02011140142R1