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

Pentazocine Lactate Injection IP 30 mg/ml

ZOCIFIX™ 30 mg

Each ml contains:

Pentazocine Lactate IP eq. to. Pentazocine.	30 mg
Benzyl Alcohol IP (As preservative)	1.5%
Water for Injections IP	q.s.

DESCRIPTION:

Pentazocine lactate is an agonist at the kappa and sigma opioid receptors and has a weak antagonist action at the mu receptor. The chemical name of pentazocine lactate is (1R,9R,13R)-1,13-dimethyl-10-(3-methylbut-2-enyl)-10-azatricyclo [7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-4-ol;2-hydroxypropanoic acid. The molecular formula is $C_{22}H_{33}NO_4$ and molecular weight is 375.5 g/mol.

THERAPEUTIC INDICATIONS

For the relief of moderate to severe pain, pre-operative or post-operative medication, as a supplement to surgical anesthesia.

POSOLOGY AND METHOD OF ADMINISTRATION

Posology

If frequent daily injections are needed over long periods, the intramuscular route is preferable to the subcutaneous. To reduce the risk of local tissue damage, injection sites should be systematically varied.

Adults and children 12 to 16 years: 45 to 60 mg IM or SC or 30 mg IV every three to four hours if required. Dosages in excess of 60 mg IM or SC or 30 mg IV are not recommended. Not more than 360 mg per day should be given.

Children 1 – 12 years: Clinical experience with parenteral pentazocine for paediatric use has been limited mainly to single dose administration for anaesthetic premedication or supplementation and postoperative analgesia for less than one week.

Single doses should not exceed 1 mg/kg body weight subcutaneously or intramuscularly or 0.5 mg/kg body weight intravenously. Where repeat doses are needed these should be given at intervals of 6 hours or longer.

Mild (non-narcotic) analgesia may be used concurrently with Pentazocine Injection.

Elderly: As impaired renal or hepatic function is often associated with aging and thus bioavailability increased, elderly patients may require smaller and/or less frequent doses of Pentazocine.

Do not use if any particle, leakage or breakage found.

CONTRAINDICATIONS

Pentazocine should not be administered to patients with established respiratory depression especially in the presence of cyanosis and excessive bronchial secretion and is also contraindicated in the presence of acute alcoholism, head injuries, conditions in which intracranial pressure is raised, acute bronchial asthma, in heart failure secondary to chronic lung disease, and in patients known to be hypersensitive to pentazocine or any excipient.

Pentazocine should be given with caution to patients prone to seizures. In cases of liver disease or cirrhosis there is an enhanced availability and the dose should be decreased. May precipitate withdrawal symptoms in patients who have recently used narcotic analgesics. Pentazocine should be used with care in patients with increased intracranial pressure and/or head injuries, or in patients with porphyria.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Particular caution should be observed in administering Pentazocine to patients with porphyria since it may provoke an acute attack in susceptible individuals as well as in its use in patients who are receiving monoamine oxidase inhibitors or who have received them within the preceding 14 days.

Pentazocine can both depress as well as elevate blood pressure possibly through the release of endogenous catecholamines. Particular caution should be observed therefore in using it in the presence of phaeochromocytoma, in the acute phase following mycardial infarction when it may increase pulmonary and systemic arterial pressure and vascular resistance, and in other clinical situations where alteration of vascular resistance and blood pressure might be particularly undesirable.

Caution should be observed in patients with renal or hepatic impairment and in elderly patients, since pentazocine metabolism may be decreased and therefore bioavailability increased. Side effects may be accentuated.

When pentazocine is administered parenterally local effects have been reported at the site of injection.

Caution should be observed in patients who are prone to seizures. Patients taking other opioids or who are opioid-dependent should also be treated cautiously since the weak opioid antagonistic effects of pentazocine may provoke withdrawal symptoms.

Caution should also be observed in patients with hypothyroidism, adrenocortical insufficiency, prostatic hypertrophy, inflammatory or obstructive bowel disorders, cholecystitis, pancreatitis or other unidentified abdominal pain.

In chronic usage, care should be exercised to avoid any unnecessary increase in dosage since prolonged use of high doses of pentazocine may produce dependence. Patients with a history of drug abuse should be closely supervised when receiving pentazocine. Cases of myositis after long term administration were reported.

Dependence Liability: Pentazocine may cause physical and psychological dependence. Patients with a history of dependence should be closely supervised. Withdrawal symptoms may occur, even in newborns after prolonged administration during pregnancy.

Abrupt discontinuation of pentazocine in patients receiving large parenteral doses over a prolonged period of time may result in withdrawal symptoms which can also occur in the newborn following prolonged in utero exposure to pentazocine. This abstinence syndrome of pentazocine is not typical of opiate dependence. Symptoms include mild abdominal cramps, nausea, vomiting, nervousness or restlessness, dizziness, fever, chills, rhinorrhoea and lacrimation. Managing the abstinence syndrome of pentazocine has raised few problems.

Supportive therapy with tranquillisers may sometimes be required. If problems occur, treatment with pentazocine should be reinstated followed by a slower rate of withdrawal. It should be emphasised that the majority of patients reported to have become dependent on pentazocine had previously been dependent on opiates or had misused other drugs. If used in myocardial infarction a small intravenous dose of pentazocine is preferable as a larger (i.e. 60 mg) dose may cause a rise in pulmonary artery pressure.

Because of the possibility of incompatibility, it should not be mixed with diazepam, aminophylline, chlordiazepoxide or soluble barbiturates.

Pentazocine should be used with caution in shock, in reduced doses in elderly and debilitated patients, in hypothyroidism, adrenocortical insufficiency, impaired liver function and prostatic hypertrophy.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND FORMS OF INTERACION

Concomitant use of monoamine oxidase inhibitors (MAOIs) with pentazocine may cause CNS excitation and hypertension through their respective effects on catecholamines. Caution, should therefore, be observed in administering Pentazocine Injection to patients who are currently receiving MAOIs or who have received them in the preceding 14 days.

Agents with sedative action including phenothiazines, tricyclic antidepressants and ethyl alcohol can enhance the central depressant effects of pentazocine, which are opposed by respiratory stimulants such as doxapram. Tobacco smoking appears to enhance the metabolic clearance rate of pentazocine reducing the clinical effectiveness of a standard dose. Pentazocine can antagonise the effects of stronger opioid agonists such as diamorphine (heroin), and morphine and is itself antagonised by naloxone. Because pentazocine has narcotic antagonist activity, it may provoke withdrawal symptoms if given to narcotic addicts, and it should be given with caution to patients recently being treated with large doses of narcotics.

PREGNANCY, LACTATION AND FERTILITY

Pregnancy: There is no epidemiological evidence for the safety of pentazocine in human pregnancy (other than during labour), but it has been widely used for many years without apparent ill consequences. In rodents, harmful effects in the foetus have been observed but only at doses high enough to cause maternal toxicity. Adrenaline should be used with

caution in patients with hyperthyroidism, diabetes mellitus, phaeochromocytoma, narrow angle glaucoma, hypokalaemia, hypercalcaemia, severe renal impairment, prostatic adenoma leading to residual urine, cerebrovascular disease, organic brain damage or arteriosclerosis, in elderly patients, in patients with shock (other than anaphylactic shock) and in organic heart disease or cardiac dilatation (severe angina pectoris, obstructive cardiomyopathy, hypertension) as well as most patients with arrhythmias. Anginal pain may be induced when coronary insufficiency is present.
Repeat administration may produce local necrosis at the sites of injection. Prolonged administration may produce metabolic acidosis, renal necrosis and adrenaline fastness or tachyphylaxis.
Adrenaline should be avoided or used with extreme caution in patients undergoing anaesthesia with halothane or other halogenated anaesthetics, in view of the risk of inducing ventricular fibrillation.
Do not mix with other agents unless compatibility is known.
Adrenaline should not be used during the second stage of labour. Accidental intravascular injection may result in cerebral haemorrhage due to the sudden rise in blood pressure. Adrenaline 1 in 1000 should not be diluted to 1 in 10,000 for use in cardiac resuscitation - when the 1 in 10,000 strength of adrenaline is Pentazocine can rapidly cross the placental barrier and enter the foetal circulation and has the potential to cause opioid effects including central depression and abstinence syndrome in the foetus and newborn infant. It does not appear to have significant adverse effects on uterine function at parturition. Nonetheless, careful consideration should be given to the use of pentazocine during pregnancy, particularly during the first trimester, or at term. Special attention should be paid to clinical monitoring of the newborn, particularly premature infants, if pentazocine has been used during labour.
Lactation: Pentazocine is excreted in very small amounts in breast milk. Caution should therefore be observed in administering pentazocine to breast-feeding mothers, particularly of infants at risk.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Pentazocine Injection IP may produce sedation, dizziness, and occasionally euphoria, so ambulant patients should be warned not to operate machinery or drive if affected. (Moderate Influence)

UNDESIRABLE EFFECTS
At normal therapeutic doses side effects are generally of a minor nature. The most frequent side effects are lightheadedness, dizziness, nausea and vomiting, sedation and sweating. The following side effects have also been reported.
Cardiovascular: Transient hypertension, tachycardia, hypotension, circulatory depression.
Central and peripheral nervous system: Hallucinations, disturbances of vision, headache, disorientation, mood changes, nightmares, insomnia, paraesthesia, syncope, euphoria, grand mal convulsions, raised intracranial pressure, confusion, tremor.
Dermatologic/Allergic: Soft tissue induration, nodules, cutaneous depression at injection sites, ulceration (sloughing) and severe sclerosis of the skin and subcutaneous tissues (and, rarely, underlying muscle), sting on injection. Allergic reactions sometimes severe have been reported including oedema of the face or anaphylactic shock, flushed skin including facial plethora, dermatitis including pruritus, toxic epidermal necrolysis, erythema multiforme.
Gastrointestional: Constipation, dry mouth, biliary tract spasm, abdominal pain.
Haematologic: Depression of white blood cell count, especially granulocytes, which is usually reversible, moderate transient eosinophilia.
Ophthalmic: Miosis
Respiratory: Respiratory depression.
Other: Urinary retention, muscle tremor, chills, alterations in rate or strength of uterine contractions during labor have also been reported at doses above 60 mg.
Marked respiratory depression with increased blood pressure and tachycardia may occur. Other side effects are changed uterine contractions, insomnia, vision disturbances, transient eosinophilia, chills and allergic reactions. Injection site should be varied as multiple doses may cause extensive fibrosis of subcutaneous and muscular tissue. Large intravenous doses may cause grand mal convulsions.

OVERDOSE
The symptoms and clinical signs of pentazocine overdose will resemble those of morphine and other opioids. They may therefore include somnolence, respiratory depression, hypotension, hypertension, tachycardia, hallucinations, or seizures. Circulatory failure and deepening coma may occur in more severe cases, particularly in patients who have also ingested other CNS depressants such as alcohol, sedatives / hypnotics, or antihistamines. Adequate measures to maintain ventilation and general circulatory support should be employed. Gastric lavage and gastric aspiration should be considered where appropriate.
For respiratory depression due to overdosage or unusual sensitivity to pentazocine, parenteral naloxone is a specific and effective antagonist. Initial doses of 0.4 to 2.0mg of naloxone are recommended, repeated at 2-3-minute intervals if needed, up to a total of 10mg. Anti-convulsant therapy may be necessary.
Other treatment should be symptomatic and supportive.

CLINICAL PHARMACOLOGY
Pharmacodynamic properties:
Pharmacotherapeutic group: analgesics
ATC Code: N02AD01
The major effect of Pentazocine is exerted on the CNS and smooth muscle. The CNS effects correspond to those of the opioids, namely analgesia, sedation and respiratory depression.
Pentazocine has analgesic and sedative actions resembling morphine. The opioid effects appear to be dose related. Pentazocine given orally or rectally is approximately one third as potent as when given intramuscularly. Speed of onset of analgesia is quickest with intramuscular administration. Onset is sooner with rectal than oral administration. Following parenteral administration analgesia usually begins 2 to 3 minutes after intravenous injection or 15 to 20 minutes after intramuscular injection and lasts about 3 hours. After oral administration analgesia usually begins after 15 to 30 minutes and lasts about 3 hours. Following rectal administration analgesia usually lasts about 5 hours. Pentazocine is also a weak opioid antagonist, which produces incomplete reversal of the cardiovascular, respiratory and behavioural depression produced by stronger opioids.
Pharmacokinetic properties
Metabolism: Pentazocine is well-absorbed from the gastrointestinal tract. Peak plasma values occur between 1 and 3 hours after oral administration. Plasma half-life is 2 to 3 hours. Peak plasma values occur about 2.5 hours after rectal administration. Plasma half-life is 2 to 5 hours. Pentazocine is well absorbed following parenteral administration. Peak plasma values occur between 15 minutes and 1 hour after intramuscular administration. Plasma half-life is 2 to 5 hours. The volume of distribution is about 200 litres. Pentazocine crosses the placenta and appears in the cerebrospinal fluid in concentrations reaching 30 to 50% of those in plasma. It is taken up to some extent by the red blood cells. 50 to 75% is protein bound.
Elimination: Pentazocine is extensively metabolised in the liver. Up to 30% is excreted as glucuronide metabolites in the urine. Up to 13% of unchanged drug may also appear in the urine. Less than 2% of the dose is eliminated in the faeces unchanged in 48 hours. Pentazocine is excreted in breast milk.

STORAGE: Store below 25°C. Protect from light.

PRESENTATION:
Primary Packing: 1 ml clear glass ampoule USP Type-I.
Secondary Packing: Such 10 ampoules placed one PVC Try and each tray packed in printed carton along with package insert.

Mfd. By:
Bharat Parenterals Limited
Survey No. 144-A, Jarod-Samlaya Road,
Vill.: Haripura, Tal. Savli, Dist. Vadodara - 391520,
Gujarat, India.

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VARENYAM®
Varenyam Healthcare Pvt. Ltd.
FF/SF, Sun Welkin Tower-H,Harni-Halol Road,
Vadodara-390022, Gujarat, India.