1. NAME OF THE MEDICINAL PRODUCT

ZATNEP / Pentazocine Injection BP 30 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each ml contains:

Pentazocine BP (30 mg)

Water for Injections BP (- QS)

3. PHARMACEUTICAL FORM:

Liquid Injection

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications:

Pentazocine is used to relieve moderate to severe pain. Pentazocine is in a class of medications called opiate (narcotic) analgesics. It works by changing the way the brain and nervous system respond to pain.

4.2 Posology and Method of Administration

Adults

Pentazocine Injections may be administered subcutaneously, intramuscularly or intravenously. The usual starting dose is 30mg to 60mg according to the severity. The dose should be adjusted according to response and repeated as necessary every three to four hours. A dose should not normally exceed 1mg/kg body weight SC or **IM,** or 0.5mg/kg iv.

The maximum daily dose is 360mg.

Children

In the case of patients between 1 year and 12 years, the maximum single dose of parenteral Pentazocine should be calculated on the basis of lmg/kg body weight intravenously.

Pentazocine Injection is not recommended for use in children under one year. Elderly Since impaired renal or hepatic function is often associated with ageing, elderly patients may require smaller doses of Pentazocine.

4.3 Contraindications

Pentazocine Injection 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.

4.4 Special Warning and Precautions for use.

Dizziness; drowsiness; exaggerated sense of well-being; lightheadedness; nausea; redness, swelling, or irritation at injection site; vomiting. Severe allergic reactions (rash; hives; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue); blurred vision or other vision problems; confusion; fainting; hallucinations; seizures; trouble sleeping; trouble urinating; unusual weakness.

4.5 Interaction with other medicinal products and other forms of interaction

Monoamine oxidase inhibitors may enhance the opioid effects of pentazocine and the agents may interact through their respective effects on catecholamine breakdown and release. 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.

4.6 Pregnancy and Lactation

Pregnancy

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome. Available data with pentazocine in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage. In animal reproduction studies, pentazocine administered subcutaneously to pregnant hamsters during the early gestational

period produced neural tube defects (i.e., exencephaly and cranioschisis) at 4.4 times the maximum daily dose. Based on animal data, advise pregnant women of the potential risk to a fetus. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. Clinical Considerations Fetal/Neonatal Adverse Reactions Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly. Labor or Delivery Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. Pentazocine is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including Pentazocine, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression. Patients

Lactation

Risk Summary The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for pentazocine and any potential adverse effects on the breastfed infant from the underlying maternal condition. Clinical Considerations Infants exposed to pentazocine through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

4.7 Effects on ability to drive and use machines

As pentazocine may produce sedation, dizziness and occasionally euphoria, patients should be warned against the performance of potentially hazardous tasks such as driving a car or operating machinery; alcohol may potentiate the sedative effect. This medicine can impair cognitive function and can affect a patient's ability to drive safely. 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

Slow or fast heartbeat • Seizures • Unusual weakness • Confusion • Hallucinations (seeing or hearing things that are not really there)

Lightheadedness or fainting spells • Nervousness or restlessness • Constipation • Decrease or difficulty passing urine • Dry mouth • Headache • Itching

4.9 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 over dosage 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.

5.1 PHARMACOLOGICAL PROPERTIES

Mechanism of Action

Pentazocine is a mixed agonist-antagonist at opioid receptors. Pentazocine is partial agonist at the mu opioid receptor and an agonist at the kappa opioid receptor.

Pharmacodynamics

Effects on the Central Nervous System

Pentazocine produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in carbon dioxide tension and electrical stimulation.

Pentazocine causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Pentazocine causes a reduction inmotility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasmresulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasmof sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System

Pentazocine produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilationmay include pruritus, flushing, red eyes and sweating and/or orthostatic hypotension.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date.

Effects on the Immune System

Opioids have been shown to have a variety of effects on components of the immune system in *in vitro* and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration–Efficacy Relationships

Pentazocine is a potent analgesic and 30 mg is usually as effective an analgesic as morphine 10 mg or meperidine 75 mg to 100 mg; however, a few studies suggest the Pentazocine to morphine ratio may range from 20 mg to 40 mg Pentazocine to 10 mg morphine. The duration of analgesia may sometimes be less than that of morphine. Analgesia usually occurs within 15 to 20 minutes after intramuscular or subcutaneous injection and within 2 to 3 minutes after intravenous injection. Pentazocine weakly antagonizes the analgesic effects of morphine, meperidine, and phenazocine; in addition, it produces incomplete reversal of cardiovascular, respiratory, and behavioral depression induced by morphine and meperidine. Pentazocine has about 1/50 the antagonistic activity of nalorphine. It also has sedative activity.

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. The minimum effective analgesic concentration of pentazocine for any individual patient may increase over time due to an

increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance.

Concentration–Adverse Reaction Relationships

There is a relationship between increasing pentazocine plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse.

5.2 Pharmacokinetics

Pentazocine is metabolized in the liver and excreted primarily in the urine.

Clinical data indicate that differences in various pharmacokinetic parameters may be observed with increasing age. In one study, elderly patients exhibited a longer mean elimination half-life, a lower mean total plasma clearance, and a larger mean area under the concentration-time curve than younger patients.

5.3 Preclinical safety data

Not available

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients

Sodium Chloride, Lactic acid, Water for Injections.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months from the date of manufacture.

6.4 Special precautions for storage

Store below 30°C, protected from light. Do not freeze.

6.5 Nature and contents of container

10 x 1 ml ampoule in a carton.

6.6 Instructions for use and handling

Keep out of reach of children.

7. MARKETING AUTHORISATION HOLDER

Manufactured By:

KILITCH DRUGS (INDIA) LTD.

Plot no. C-301/2, M.I.D.C, T.T.C Industrial Area, Pawane, Navi Mumbai - 400705, Maharashtra ,INDIA.

8. MARKETING AUTHORITY:

DAITECH PHARMACEUTICALS LTD.

10 Faranah St, Wuse Zone 2, Abuja, NIGERIA