ALLBIO PENTAZOCINE (Pentazocine Injection BP)

Summary Product Characteristics (SPC)

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

ALLBIO PENTAZOCINE (Pentazocine Injection BP)

Strength

Each ml Contains :

Pentazocine (As Lactate) BP	30 mg
Sodium Chloride BP	2.8 mg
Water for Injections BP	Q.S

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sr. No.	Name of raw material	Specification	Label Claim (mg/ml)	Qty./Ampoules (mg/ml)	Purpose of use
1.	Pentazocine	BP	30	30.000	Active
2.	Lactic Acid	BP	-	0.012 ml	pH Adjustment
3.	Sodium Chloride	BP	2.8	2.800	Tonicity agent
4.	Water For injection	BP	-	Q.S.	Solvent

BP : British Pharmacopoeia

3. PHARMACEUTICAL FORM

Parenteral form for Intramuscular (IM), Intravenous (IV) and subcutaneous (SC)

A colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pentazocine 30 mg Injection is a potent analgesic medicine used in the treatment of moderate to severe pain for which alternative treatments are inadequate. This medicine is also used as a pre-anesthetic or preoperative medication and as a supplement to surgical anesthesia. This medicine should be used with extreme caution due to the increased risk of addiction.

4.2 Posology and method of administration

Hepatic Impairment

Dosage should be modified depending on clinical response and degree of hepatic impairment, but no quantitative recommendations are available. If repeated doses are required, the dosing interval should be lengthened or the dosage reduced.

Renal Impairment

CrCl> 50 ml/min: no dosage adjustment required.
CrCl 10—50 ml/min: reduce dose by 25%.
CrCl< 10 ml/min: reduce dose by 50%.

Injectable Administration

May be administered by intravenous, intramuscular, or subcutaneous injection. However, the subcutaneous route should be used only when necessary, due to possible severe damage at injection sites.
No dilution is necessary.
Visually inspect parenteral products for particulate matter and discoloration prior to administration whenever solution and container permit.

Intravenous Administration

Inject directly into a vein or into tubing of a free-flowing compatible IV infusion.

Intramuscular Administration

Inject deeply into a large muscle mass. Aspirate prior to injection to avoid injection into a blood vessel.
Rotation of intramuscular injection sites (e.g., upper outer quadrants of the buttocks, mid-lateral aspects of the thighs, and the deltoid areas) is essential to decrease risk of severe tissue damage at injection sites.

Subcutaneous Administration

Administer subcutaneously only when necessary, as there is the possibility of severe tissue damage at injection sites. When frequent injections are needed, administer intramuscularly.
Rotation of injection sites (e.g., upper outer quadrants of the buttocks, mid-lateral aspects of the thighs, and the deltoid areas) is essential to reduce the risk of tissue damage.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed.

- Pentazocine should not be administered to patients with established respiratory depression, especially in the presence of cyanosis and excessive bronchial secretion
- Acute alcoholism
- Acute bronchial asthma
- Heart failure secondary to chronic lung disease
- Porphyria
- Raised intracranial pressure, head injuries or pathological brain conditions where clouding of the sensorium is undesirable.

4.4 Special warnings and precautions for use

Pentozocine can both depress as well as elevate blood pressure possibly through the release of endogenous catecholamines.

Particular caution should be observed in patients with phaeochromocytoma, in the acute phase following myocardial infarction when it may increase pulmonary and systemic arterial pressure and vascular resistance, and in other clinical situations where alterations of vascular resistance and blood pressure might be particularly undesirable.

Caution should be exercised when administering high doses of pentazocine to patients who have suffered a recent myocardial infarction due to increases in heart rate and blood pressure.

Pentazocine should be given with caution to patients with severely impaired renal or hepatic function and in elderly patients, who may additionally be especially sensitive to the effects of opioids, as both conditions may lead to an increase in bioavailability of pentazocine and call for a reduction in dosage.

Administer with caution to patients previously on large doses of narcotics.

Cautions should be observed in patients who are prone to seizures.

Patients taking other opioids should be treated cautiously and pentazocine should not be used on patients already dependent on other opioids 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.

When pentazocine is prescribed for chronic use, the physician should take precautions to avoid any unnecessary increase in dose by the patient since prolonged use of high doses of pentazocine may produce a dependence.

Patients with a history of drug abuse should be closely supervised when receiving pentazocine.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:
Concomitant use of Pentazocine and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks,

concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Pentazocine concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms.

Some opioids can cause CNS excitation or depression. Pentazocine, like most other strong analgesics, should not be used in patients who are receiving monoamine oxidase inhibitors or who have received them within the past 14 days. Opioids can be taken after two weeks of MAOI's discontinuation

After long term treatment (> 3 months) of analgesics with use every second day or more frequently, headache may develop or aggravate. Headache caused by overuse of analgesics (MOH - medication-overuse headache) should not be treated by increasing the dose. In such cases the use of analgesics should be discontinued in consultation with a doctor.

DEPENDENCE LIABILITY

There have been rare reports of mild withdrawal symptoms in the new-born after prolonged maternal use of pentazocine during pregnancy. This abstinence syndrome of pentazocine is not typical of opiate dependence. Symptoms include mild abdominal cramps, nausea, vomiting, nervousness or restlessness, dizziness, fever and chills, but are mild compared with opiate withdrawal symptoms. Withdrawal of pentazocine from such patients has caused few problems only occasionally requiring treatment with tranquillisers. It should be emphasised that the majority of patients reported to have become dependant on pentazocine had previously been dependant on opiates or had misused other drugs.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactosemalabsorption should not take this medicine.

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.

Pentazocine, should not be used in patients who are receiving monoamine oxidase inhibitors or who have received them within the past 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 of pentazocine.

Pentazocine can antagonise the effects of stronger opioid agonists such as diamorphine (heroin) and morphine, and may provoke withdrawal symptoms if given to narcotic addicts and is itself antagonised by naloxone.

Sedative medicines such as benzodiazepines or related drugs:

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Pentazocine is classified as FDA pregnancy category C. Patients receiving injectable pentazocine during labor have experienced no adverse effects other than those that occur with commonly used analgesics. Use with caution during the obstetric delivery of premature infants. Administration during obstetric delivery may result in respiratory depression in the newborn, and pentazocine can cross the placental barrier and also cause central nervous system depression in the newborn. Outside of labor and delivery, pentazocine should be used during pregnancy only if clearly needed. Animal studies have not demonstrated teratogenic or embryotoxic effects. Further, prolonged maternal use of opioids, such as pentazocine, during pregnancy may result in neonatal opioid withdrawal syndrome (NOWS). This syndrome can be life-threatening. Severe symptoms may require pharmacologic therapy managed by clinicians familiar with neonatal opioid withdrawal. Monitor the neonate for withdrawal symptoms including irritability, hyperactivity, abnormal sleep pattern, high-pitched crying, tremor, vomiting, diarrhea, and failure to gain weight. Onset, duration, and severity of opioid withdrawal may vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination by the newborn.

Breast-feeding

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.

It is recommended that infants of nursing mothers who are receiving high doses of pentazocine, should be appropriately monitored.

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. 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

4.8 Undesirable effects

In chronic usage, care should be exercised to avoid any unnecessary increase in dosage since prolonged use of high dosage of pentazocine may produce dependence.

At normal therapeutic dosed, side effects are generally of a minor nature. Sedation and drowsiness, the most common effect, is less than that associated with morphine.

The most frequent side effects are light-headedness, dizziness, sedation, nausea, vomiting, and sweating.

The following side effects have also been reported.

Cardiovascular disorders: transient hypertension, tachycardia, bradycardia, hypotension, circulatory depression, palpitations.

Nervous system disorders: hallucinations may occur occasionally, dysphoria, disturbances of vision, headache, disorientation, mood changes, nightmares, insomnia, paraesthesia, syncope, euphoria, grand mal convulsions, raised intracranial pressure, confusion, muscle tremor thought disturbances.

Immune system disorders: oedema of the face, flushed skin including facial plethora, skin rashes, urticaria, dermatitis including pruritus, chills and allergic reactions.

Gastrointestinal disorders: constipation, dry mouth, ureteric or biliary spasm, abdominal pain

Blood and lymphatic system disorders: depression of the white blood cell count, especially granulocyctes, which is usually reversible, moderate transient eosinophillia.

Eye disorders: miosis, disturbances of vision.

Respiratory, thoracic and mediastinal disorders: respiratory depression.

Skin and subcutaneous system disorders: toxic epidermal necrolysis.

Renal and urinary disorders: urinary retention, ureteric tract spasm.

Pregnancy, puerperium and perinatal conditions: alterations in rate or strength of uterine contractions during labour.

Reproductive system and breast disorders: decreased libido or potency.

General disorders and administration site conditions: hypothermia.

4.9 Overdose

The symptoms 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, as may convulsions, 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 dose of 0.4 to 0.2mg of naloxone are recommended, repeated at 2-3 minute intervals if needed, up to a total of 10 mg. Anti-convulsant therapy may be necessary

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Benzomorphan derivatives

ATC code: N02AD

Pentazocine is a mixed agonist-antagonist at opiate receptors. Only the l-isomer of pentazocine has analgesic activity; the d-isomer has little affinity for opiate receptors. Opiates are believed to exert their analgesic effects by stimulating specific opiate receptors, designated as mu, kappa, and delta, which have been reclassified by an International Union of Pharmacology subcommittee as OP1 (delta), OP2 (kappa), and OP3 (mu). Mu-receptors are considered the classic morphine-receptor type, and stimulation at this receptor produces supraspinal analgesia, respiratory depression, euphoria, and physical dependence. Pentazocine is an agonist at kappa-receptors but is a weak antagonist or partial agonist at mu-receptors. Actions at kappa-receptors are believed to produce alterations in the perception of pain, as well as the emotional response to pain. Pentazocine's antagonism at the mu-receptor is weaker than both butorphanol and nalbuphine. Pentazocine may have some agonistic effects at the mu-receptor, due to the morphine-like euphoria seen after therapeutic doses. It does not antagonize the respiratory depressive effects of morphine. However, when given to patients physically dependent on pure opiate agonists, pentazocine will decrease analgesia and may precipitate a withdrawal reaction. Since pentazocine is less active at the mu-receptor, it produces less respiratory depression and may pose a lower risk of physical dependence than morphine. Pentazocine has little effect on bile duct flow and duodenal smooth muscle activity. The dysphoric and psychotomimetic effects of pentazocine are due to activity at sigma opiate receptors. Cardiovascular responses to pentazocine are different from other opiates. Therapeutic doses generally cause an increase in blood pressure and heart rate. Therefore, pentazocine is not recommended for pain due to acute myocardial infarction, since it may simultaneously increase pulmonary arterial and central venous pressure, and thus, increase cardiac workload.

The pharmacologic effects observed after opiates bind to their receptors might involve a second messenger such as cyclic AMP, which is synthesized by adenylate cyclase. Opioid receptors are coupled to these second messenger systems through an inhibitory G-protein (guanine nucleotide-binding protein). G-proteins are located at the cell surface along with many other receptors, including opioid receptors. G-proteins are thought to interact with opiate receptors, giving the receptor a higher affinity for the opiate. Binding of the opiate stimulates the exchange of guanosine triphosphate (GTP) for guanosine diphosphate (GDP) on the G-protein complex. Binding of GTP leads to a release of the G-protein subunit, which acts on the effector system. In this case, the effector system is adenylate cyclase and

cyclic AMP located at the inner surface of the plasma membrane. Opioid agonists effectively inhibit adenylate cyclase and cause a decrease in intracellular cyclic AMP levels. Other research has shown that mu-, delta-, and kappa-receptors are associated with ion channels and control the influx of cations into the cell. Mu- and delta-receptor stimulation is associated with increasing potassium influx, and kappa-receptor activity is associated with reducing calcium influx in cells located in various human and animal nerve systems. All of these effects appear to ultimately reduce transmitter release, and may also be mediated through G-proteins.

5.2 Pharmacokinetic properties

Pentazocine is given parenterally via intravenous (IV), intramuscular (IM), or subcutaneous (SC) injection.
Pentazocine is distributed into fetal circulation. It undergoes hepatic metabolism via oxidation and glucuronidation. A small amount of unchanged pentazocine and its metabolites are excreted in the urine. Data suggest that pentazocine is recirculated through the biliary system. The elimination half-life was measured as 3.6 hours (range 1.5 to 10 hours) in 24 healthy volunteers. Approximately 60% of the total dose is eliminated within 24 hours.

Intravenous Route
Following IV injection of pentazocine, the onset of analgesia is 2—3 minutes. The duration of analgesia is 2—3 hours.

Intramuscular Route
Following IM injection of pentazocine, the onset of analgesia is 15—20 minutes. The duration of analgesia is 2—3 hours.

Subcutaneous Route
Following SC injection of pentazocine, the onset of analgesia is 15—20 minutes.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactic Acid	BP
Sodium Chloride	BP
Water For injection	BP

6.2 Incompatibilities

Pentazocine Injection BP is administered by intravenous, intramuscular, or subcutaneous injection. However, the subcutaneous route should be used only when necessary, due to possible severe damage at injection sites.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30° C. Protect from light.

6.5 Nature and contents of container

10 X 1 ml Ampoule

6.6 Special precautions for disposal and other handling

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

7. APPLICANT/MANUFACTURER

MARKETING AUTHORISATION HOLDER
ALLBIO HEALTHCARE NIGERIA LTD.
No. 28/29, Gidan Golde, Niger Street,
Opp. Malam Kato Square,
Kano, Nigeria

MANUFACTURED
SHUKRA PHARMACEUTICALS LTD
Plot No. 795, Rakanpur Sola-Santej Road,
Ta. Kalol, Dist. Gandhinagar
Gujarat, India