SUMMARY OF PRODUCT CHARACTERISTICS

FORTWIN INJECTION
(Pentazocine Lactate Injection)

1. NAME OF THE MEDICINAL PRODUCT

Pentazocine Lactate Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains:
Pentazocine Lactate equivalent to
Pentazocine USP……. 30 mg

Excipients: see section 6.1 for full list of excipients.

3. PHARMACEUTICAL FORM

Injection

4. CLINICAL PARTICULARS [1]

4.1 Therapeutic indications

Fortwin Injection is indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. **Fortwin Injection** may also be used for preoperative or pre-anesthetic medication and as a supplement to surgical anesthesia.

Limitations of Use
Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses (see **section 4.4**), reserve **Fortwin Injection** for use in patients for whom alternative treatment options [e.g., non-opioid analgesics or opioid combination products]:

- Have not been tolerated, or are not expected to be tolerated,
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia.

4.2 Posology and method of administration

Important Dosage and Administration Instructions

Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals (see **section 4.4**).

Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse (see **section 4.4**).

Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with **Fortwin Injection** and adjust the dosage accordingly (see **section 4.4**).

Do not mix **Fortwin Injection** in the same syringe with soluble barbiturates because precipitation will occur.

Initial Dosage

Adults, Excluding Patients in Labor
The recommended single parenteral dose is 30 mg by intramuscular, subcutaneous, or intravenous route. This may be repeated every 3 to 4 hours. Doses in excess of 30 mg intravenously or 60 mg intramuscularly or subcutaneously are not recommended. Total daily dosage should not exceed 360 mg. Elderly patients may be more sensitive to the analgesic effects of **Fortwin Injection** than younger patients. Elderly patients generally should be started on low doses of **Fortwin Injection** and observed closely.

The subcutaneous route of administration should be used only when necessary because of possible severe tissue damage at injection sites (see **section 4.4**). When frequent injections are needed, the drug should be administered intramuscularly. In addition, constant rotation of injection sites (e.g., the upper outer quadrants of the buttocks, mid-lateral aspects of the thighs, and the deltoid areas) is essential.

Patients in Labor
A single, intramuscular 30 mg dose has been most commonly administered. An intravenous 20 mg dose has given adequate pain relief to some patients in labor when contractions become regular, and this dose may be given two or three times at two- to three-hour intervals, as needed.

Pediatric Patients Excluding Patients Less Than One Year Old
The recommended single parenteral dose as premedication for sedation is 0.5 mg/kg by intramuscular route.

CAUTION: Fortwin Injection should not be mixed in the same syringe with soluble barbiturates because precipitation will occur.

Initiating Treatment with ***Fortwin Injection***

There is inter-patient variability in the potency of opioid drugs and opioid formulations. Therefore, a conservative approach is advised when determining the total daily dosage of **Fortwin Injection**. It is safer to underestimate a patient's 24-hour **Fortwin Injection** dosage than to overestimate the 24-hour **Fortwin Injection** dosage and manage an adverse reaction due to overdose.

Titration and Maintenance of Therapy

Individually titrate **Fortwin Injection** to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving **Fortwin Injection** to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse (see **section 4.4**). Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration.

If the level of pain increases after dosage stabilization, attempt to identify the source of increased pain before increasing the **Fortwin Injection** dosage. If unacceptable opioid-related adverse reactions are observed, consider reducing the dosage. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

Discontinuation of Fortwin Injection

When a patient who has been taking **Fortwin Injection** regularly and may be physically dependent no longer requires therapy with **Fortwin Injection**, taper the dose gradually, by 25% to 50% every 2 to 4 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue **Fortwin Injection** in a physically-dependent patient (see **section 4.4**).

4.3 Contraindications

Fortwin Injection is contraindicated in patients with:

- Significant respiratory depression (see **section 4.4**)
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment (see **section 4.4**)
- Known or suspected gastrointestinal obstruction, including paralytic ileus (see **section 4.4**)
- Hypersensitivity to pentazocine (e.g., anaphylaxis) (see **section 4.8**)

4.4 Special warnings and precautions for use

BOXED WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse, and Misuse

Pentazocine exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing pentazocine, and monitor all patients regularly for the development of these behaviors and conditions.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of pentazocine. Monitor for respiratory depression, especially during initiation of pentazocine or following a dose increase.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of pentazocine during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Risks from Concomitant Use With Benzodiazepines or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death

- Reserve concomitant prescribing of pentazocine injection and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

Addiction, Abuse, and Misuse

Fortwin Injection contains pentazocine, a Schedule IV controlled substance. As an opioid, pentazocine exposes users to the risks of addiction, abuse, and misuse.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed pentazocine. Addiction can occur at recommended dosages and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing pentazocine, and monitor all patients receiving pentazocine for the development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as pentazocine, but use in such patients necessitates intensive counseling about the risks and proper use of pentazocine along with intensive monitoring for signs of addiction, abuse, and misuse.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing pentazocine. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status (see **section 4.9**). Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of pentazocine, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases of pentazocine.

To reduce the risk of respiratory depression, proper dosing and titration of pentazocine are essential (see **section 4.2**). Over-estimating the pentazocine dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of pentazocine during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged

period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available (see **section 4.6**).

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants
Profound sedation, respiratory depression, coma, and death may result from the concomitant use of pentazocine injection with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Concomitant use of opioid analgesics and benzodiazepines has been reported to increase the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics (see **section 4.5**).

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when pentazocine injection is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advice patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs (see **section 4.5**).

Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients
The use of pentazocine in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: Pentazocine -treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of pentazocine.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating pentazocine and when pentazocine is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients.

Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Severe Hypotension

Pentazocine may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g. phenothiazines or general anesthetics) (see **section 4.5**). Monitor these patients for signs of hypotension after initiating or titrating the dosage of pentazocine. In patients with circulatory shock, pentazocine may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of pentazocine in patients with circulatory shock.

Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

In patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), pentazocine may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with pentazocine.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of pentazocine in patients with impaired consciousness or coma.

Risks of Use in Patients with Gastrointestinal Conditions

Pentazocine is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

Pentazocine may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis for worsening symptoms.

Increased Risk of Seizures in Patients with Convulsive or Seizure Disorders

Pentazocine may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during pentazocine therapy.

Withdrawal

The use of pentazocine, a mixed agonist/antagonist opioid analgesic, in patients who are receiving a full opioid agonist analgesic may reduce the analgesic effect and/or precipitate withdrawal symptoms. Avoid concomitant use of pentazocine with a full opioid agonist analgesic.

When discontinuing pentazocine in a physically-dependent patient, gradually taper the dosage (see **section 4.2**). Do not abruptly discontinue pentazocine in these patients.

Tissue Damage at Injection Sites

Severe sclerosis of the skin, subcutaneous tissues, and underlying muscle have been reported to occur at the injection sites of patients who have received multiple doses of pentazocine lactate. Constant rotation of injection sites is, therefore, essential. In addition, pentazocine has been reported to be tolerated less well subcutaneously than intramuscularly (see **section 4.2**).

Myocardial Infarction

Caution should be exercised in the intravenous use of pentazocine for patients with acute myocardial infarction accompanied by hypertension or left ventricular failure. Intravenous administration of pentazocine has been reported to increase systemic and pulmonary arterial pressure and systemic vascular resistance in patients with acute myocardial infarction.

Impaired Renal or Hepatic Function

Although reported laboratory tests have not indicated that pentazocine causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease appears to predispose to greater side effects (e.g., marked apprehension, anxiety, dizziness, sleepiness) from the usual clinical dose, and may be the result of decreased metabolism of the drug by the liver.

Biliary Surgery

Narcotic drug products are generally considered to elevate biliary tract pressure for varying periods following their administration. Some reported evidence suggests that pentazocine may differ from other marketed narcotics in this respect (i.e., it causes little or no elevation in biliary tract pressures). The clinical significance of these findings, however, is not yet known.

Pediatric Use

The safety and efficacy of pentazocine as preoperative or preanesthetic medication have been reported to be established in pediatric patients 1 to 16 years of age. The safety and efficacy of pentazocine as a premedication for sedation have not been established in pediatric patients less than one year old. Reported information on the safety profile of pentazocine as a postoperative analgesic in children less than 16 years is limited.

Geriatric Use

Pentazocine is metabolized in the liver and excreted primarily in the urine. Patients with impaired renal or hepatic function may have slower elimination of the drug, and the risk of adverse reactions to this drug may be greater in these patients. Elderly patients (aged 65 years or older) may have increased sensitivity to pentazocine. In general, use caution when selecting a dosage for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has been reported to occur after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of pentazocine slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression. Pentazocine is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Drug abuse and dependence

Controlled Substance

Fortwin Injection contains pentazocine, a Schedule IV controlled substance.

Abuse

Fortwin Injection contains pentazocine, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone and tapentadol. **Fortwin Injection** can be abused and is subject to misuse, addiction, and criminal diversion.

All patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

"Drug-seeking" behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated "loss" of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating health care provider(s). "Doctor shopping" (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Health care providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

Pentazocine, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to Abuse of Pentazocine Injection

Injection Abuse of pentazocine poses a risk of overdose and death. The risk is increased with concurrent abuse of pentazocine with alcohol and other central nervous system depressants.

Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Dependence
Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (butorphanol, nalbuphine), or partial agonists (e.g. buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

Pentazocine injection should not be abruptly discontinued in a physically-dependent patient (see **section 4.2**). If pentazocine is abruptly discontinued in a physically-dependent patient, a withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs (see **section 4.6**).

Sodium
This medicinal product contains mg sodium per dose. To be taken into consideration by patients on a controlled sodium diet" should be incorporated.

Patient counseling information

Serotonin Syndrome
Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their physicians if they are taking, or plan to take serotonergic medications (see **section 4.5)**.

Constipation
Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention (see **section 4.8**, **section 5)**.

4.5 Interaction with other medicinal products and other forms of interaction

Table below includes clinically significant drug interactions reported with pentazocine.

Benzodiazepines and other Central Nervous System (CNS) Depressants	
Clinical Impact	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.
Intervention	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see **section 4.4**).
Examples	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
Clinical Impact	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Intervention	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue pentazocine if serotonin syndrome is suspected.
Examples	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that effect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact	May reduce the analgesic effect of pentazocine and/or precipitate withdrawal symptoms.
Intervention	Avoid concomitant use
Examples	Butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
Clinical Impact	Pentazocine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of pentazocine and/or the muscle relaxant as necessary.
Diuretics	
Clinical Impact	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.

Anticholinergic Drugs	
Clinical Impact	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention	Monitor patients for signs of urinary retention or reduced gastric motility when pentazocine is used concomitantly with anticholinergic drugs.

4.6 Pregnancy and lactation

Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome. Reported data with pentazocine in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage.

Pentazocine administered subcutaneously to pregnant hamsters during the early gestational period has been reported to produce neural tube defects (i.e., exencephaly and cranioschisis) at 4.4 times the maximum daily dose [see Data]. Based on reported animal data, advice 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.

The estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies has been reported to be 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 (see **section 4.4**).

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 receiving pentazocine during labor has been reported to experience no adverse effects other than those that occur with commonly used analgesics.

Data

Animal Data
In a published report, a single dose of pentazocine administered to pregnant hamsters on Gestation Day 8 increased the incidence of neural tube defects (exencephaly and cranioschisis) at a dose of 196 mg/kg, SC (4.4-times the maximum daily dose (MDD) of 360 mg/day pentazocine on a body surface area basis). No evidence of neural tube defects were reported following a dose of 98 mg/kg (2.2 times the MDD).

Lactation

Risk Summary
The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for pentazocine and any potential adverse effects on the breastfed infant from pentazocine or 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.

Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible (see **section 4.8**).

4.7 Effects on ability to drive and use machines

Pentazocine may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive

or operate dangerous machinery unless they are tolerant to the effects of pentazocine and know how they will react to the medication (see **section 4.4**).

4.8 Undesirable effects

The following serious adverse reactions are described, or described in greater detail, in other sections:

- Addiction, Abuse, and Misuse (see **section 4.4**)
- Life-Threatening Respiratory Depression (see **section 4.4**)
- Neonatal Opioid Withdrawal Syndrome (see **section 4.4**)
- Interactions with Benzodiazepines or Other CNS Depressants (see **section 4.4**)
- Adrenal Insufficiency (see **section 4.4**)
- Severe Hypotension (see **section 4.4**)
- Gastrointestinal Adverse Reactions (see **section 4.4**)
- Seizures (see **section 4.4**)
- Withdrawal (see **section 4.4**)

The following adverse reactions have been reported with the use of pentazocine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The most commonly occurring reactions were nausea, dizziness or lightheadedness, vomiting, euphoria.

Dermatologic Reactions: Soft tissue induration, nodules, and cutaneous depression can occur at injection sites. Ulceration (sloughing) and severe sclerosis of the skin and subcutaneous tissues (and, rarely, underlying muscle) have been reported after multiple doses. Other reported dermatologic reactions include diaphoresis, sting on injection, flushed skin including plethora, dermatitis including pruritus.

Infrequently occurring reactions are:
Respiratory: respiratory depression, dyspnea, transient apnea in a small number of newborn infants whose mothers received pentazocine during labor;

Cardiovascular: circulatory depression, shock, hypertension;

CNS effects: dizziness, lightheadedness, hallucinations, sedation, euphoria, headache, confusion, disorientation; infrequently weakness, disturbed dreams, insomnia, syncope, visual blurring and focusing difficulty, depression; and rarely tremor, irritability, excitement, tinnitus;

Gastrointestinal: constipation, dry mouth;

Other: urinary retention, headache, paresthesia, alterations in rate or strength of uterine contractions during labor.

Rarely reported reactions include:
Neuromuscular and psychiatric: muscle tremor, insomnia, disorientation, hallucinations; gastrointestinal: taste alteration, diarrhea and cramps;

Ophthalmic: blurred vision, nystagmus, diplopia, miosis; hematologic: depression of white blood cells (especially granulocytes), which is usually reversible, moderate transient eosinophilia;

Other: tachycardia, weakness or faintness, chills; allergic reactions including edema of the face, toxic epidermal necrolysis.

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

Anaphylaxis: Anaphylaxis has been reported.

Androgen deficiency: Cases of androgen deficiency have been reported with chronic use of opioids (see **section 5.1 and 5.2**)**.**

4.9 Overdose

Clinical Presentation

Acute overdose with pentazocine can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations (see **section 5**).

Treatment of Overdose

In case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary

edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support techniques.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

5. PHARMACOLOGICAL PROPERTIES [1]

5.1 Pharmacodynamic 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.

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 in motility 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 spasm resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of 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 vasodilation may 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 (see **section 4.8**).

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 reported to date (see **section 4.8**).

Effects on the Immune System
Opioids have been reported to have a variety of effects on components of the immune system. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive (see **section 4.2**).

Concentration–Efficacy Relationships
Pantazocine 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, pantazocine to morphine ratio has been reported to be in range from 20 mg to 40 mg pantazocine 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. Pantazocine 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. Pantazocine 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 (see **section 4.2**). 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 reactions (see **section 4.2**).

5.2 Pharmacokinetics properties

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

Reported clinical data indicate that differences in various pharmacokinetic parameters may be observed with increasing age. Elderly patients has been reported to exhibit 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

None reported

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactic Acid BP…….11.4µl
Sodium Chloride BP……2.80
Water for injection USP ….q.s. to make 1.0 ml

6.2 Incompatibilities

None

6.3 Shelf life

48 months

6.4 Special precautions for storage

Store below 30ºC, Protect from light

6.5 Nature and contents of container

1 ml clear glass ampoule

6.6 Special precautions for disposal and other handling

Keep all medicines out of the reach of children

7. MARKETING AUTHORISATION HOLDER

Ranbaxy Nigeria Limited

8. MARKETING AUTHORISATION NUMBER(S)

04-0789

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02-Apr-1997

10. DATE OF REVISION OF THE TEXT

December 2023

REFERENCES

1. Prescribing Information of TALWIN® INJECTION, Hospira Inc., USA, July, 2023.

TALWIN® is a registered trademark of Hospira Inc. The makers of this brand is not associated with and do not endorse Sun Pharmaceutical Industries Ltd. or its products.

Online coding shall be done during packaging with GTIN, batch details and serial no. in 2 D data matrix Barcode

GTIN
Lot
Mfd
Exp
S.N.

This Serial number will be unique for each pack

UNWINDING DIRECTION

ZAN

Keep all medicines out of the reach of children.

NAFDAC Reg. No.: 04-0789

FORTWIN®

5143470

PENTAZOCINE INJECTION 30 mg USP
100 x 1ml

FOR INTRAMUSCULAR, INTRAVENOUS AND SUBCUTANEOUS USE.

Mfg. Lic. No.: KD/443-A

Manufactured for
Sun Pharmaceutical Ind. Ltd.
By: Samrudh Pharmaceuticals Pvt. Ltd.
J-174, M.I.D.C., Tarapur Boisar,
Dist. Thane 401 506, India

Marketed by:
Ranbaxy Nigeria Ltd.
a SUN PHARMA company
1st Floor, Abimbola House,
24, Abimbola Street,
Ilasamaja, Isolo, Lagos,
Nigeria

SUN PHARMA

Caution : Physicians may please see the warning mentioned on the package insert before prescribing the drug.
Store below 30°C, Protect from light.
Each ml contains :
Pentazocine (as lactate) USP (30 mg)
Sodium Chloride BP (2.8 mg)
Water for Injection q.s. BP (1 ml)

[5143470] - LBST FORTWIN INJ 100X1ML
MARKET - NIGE
SIZE: 246 x 100 mm
SPIL-DWS: 19.06.17US,
REFERENCE CODE : 5132268
NVZ AREA : 40 x 100 MM

Black