HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TALWIN safely and effectively. See full prescribing information for TALWIN.

TALWIN (pentazocine), injection, for intramuscular, subcutaneous, or intravenous use, CIV

Initial U.S. Approval: 1967

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

See full prescribing information for complete boxed warning.

- **TALWIN exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor regularly for these behaviors and conditions. (5.1)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. (5.2)**
- **Prolonged use of TALWIN during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.3)**
- **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 for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.4, 7)**

---------- RECENT MAJOR CHANGES ----------

Boxed Warning	12/2016
Indications and Usage (1)	12/2016
Dosage and Administration (2)	12/2016
Contraindications (4)	12/2016
Warnings and Precautions (5)	12/2016

---------- INDICATIONS AND USAGE ----------

TALWIN is a mixed agonist/antagonist indicated for

- the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.
- for use as a preoperative or preanesthetic medication and as a supplement to surgical anesthesia. (1)

Limitations of Use (1)
Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve TALWIN 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

---------- DOSAGE AND ADMINISTRATION ----------

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. (2.1)
- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)
- The recommended single parenteral dose is 30 mg by intramuscular, subcutaneous, or intravenous route. This may be repeated every 3 to 4 hours. (2.2)
- Do not abruptly discontinue TALWIN in a physically dependent patient. (2.4)

---------- DOSAGE FORMS AND STRENGTHS ----------

- Injection: 30 mg/mL Multiple-Dose Vial. (3)
- Injection: 30 mg/mL Ampul. (3)

---------- CONTRAINDICATIONS ----------

- Significant respiratory depression. (4)
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment. (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus. (4)
- Hypersensitivity to pentazocine. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.2)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.6)
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of TALWIN in patients with circulatory shock. (5.7)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of TALWIN in patients with impaired consciousness or coma. (5.8)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions were nausea, dizziness or lightheadedness, vomiting, and euphoria. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Hospira, Inc. at 1-800-441-4100, or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

---------- DRUG INTERACTIONS ----------

-
- Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue TALWIN if serotonin syndrome is suspected. (7)
- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with TALWIN because they may reduce analgesic effect of TALWIN or precipitate withdrawal symptoms. (7)

---------- USE IN SPECIFIC POPULATIONS ----------

Pregnancy: May cause fetal harm. (8.1)
Lactation: TALWIN has been detected in human milk. Closely monitor infants of nursing women receiving TALWIN. (8.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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

TALWIN 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 TALWIN, and monitor all patients regularly for the development of these behaviors and conditions *[see Warnings and Precautions (5.1)]*.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of TALWIN. Monitor for respiratory depression, especially during initiation of TALWIN or following a dose increase *[see Warnings and Precautions (5.2)]*.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of TALWIN 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 *[see Warnings and Precautions (5.3)]*.

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. *[see Warnings and Precautions (5.4), Drug Interactions (7)]*

- **Reserve concomitant prescribing of TALWIN 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.**

1 INDICATIONS AND USAGE

TALWIN is indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. TALWIN may also be used for preoperative or preanesthetic 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 Warnings and Precautions (5.1)]*, reserve TALWIN 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

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[*see Warnings and Precautions (5)*]*.

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 Warnings and Precautions (5.1)]*.

Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with TALWIN and adjust the dosage accordingly *[see Warnings and Precautions (5.2)]*.

Do not mix TALWIN in the same syringe with soluble barbiturates because precipitation will occur.

2.2 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 TALWIN than younger patients. Elderly patients generally should be started on low doses of TALWIN and observed closely.

The subcutaneous route of administration should be used only when necessary because of possible severe tissue damage at injection sites *[see Warnings and Precautions (5.13)]*. 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: TALWIN should not be mixed in the same syringe with soluble barbiturates because precipitation will occur.

Initiating Treatment with TALWIN

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 TALWIN. It is safer to underestimate a patient’s 24-hour TALWIN dosage than to overestimate the 24-hour TALWIN dosage and manage an adverse reaction due to overdose.

2.3 Titration and Maintenance of Therapy

Individually titrate TALWIN to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving TALWIN 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 Warnings and Precautions (5.1)]*. 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 TALWIN 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.

2.4 Discontinuation of TALWIN

When a patient who has been taking TALWIN regularly and may be physically dependent no longer requires therapy with TALWIN, 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 TALWIN in a physically-dependent patient *[see Warnings and Precautions (5.11), Drug Abuse and Dependence (9.3)]*.

3 DOSAGE FORMS AND STRENGTHS

- Injection: 30 mg/mL Multiple-Dose Vial
- Injection: 30 mg/mL Ampul

4 CONTRAINDICATIONS

TALWIN is contraindicated in patients with:

- Significant respiratory depression *[see Warnings and Precautions (5.2)]*
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.5)]*
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.9)]*
- Hypersensitivity to pentazocine (e.g., anaphylaxis) *[see Adverse Reactions (6.2)]*

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

TALWIN contains pentazocine, a Schedule IV controlled substance. As an opioid, TALWIN exposes users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9)]*.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed TALWIN. 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 TALWIN, and monitor all patients receiving TALWIN 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 TALWIN, but use in such patients necessitates intensive counseling about the risks and proper use of TALWIN 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 TALWIN. 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.

5.2 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 Overdosage (10)]*. 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 TALWIN, 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 TALWIN.

To reduce the risk of respiratory depression, proper dosing and titration of TALWIN are essential *[see Dosage and Administration (2)]*. Overestimating the TALWIN dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

5.3 Neonatal Opioid Withdrawal Syndrome

Prolonged use of TALWIN 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 Use in Specific Populations (8.1), Patient Counseling Information (17)]*.

5.4 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of TALWIN 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.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases 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 Drug Interactions (7)]*

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 TALWIN Injection is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise 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 Drug Interactions (7), Patient Counselling Information (17)]*.

5.5 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of TALWIN 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: TALWIN-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 TALWIN *[see Warnings and Precautions (5.2)]*.

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 *[see Warnings and Precautions (5.2)]*.

Monitor such patients closely, particularly when initiating and titrating TALWIN and when TALWIN is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.2)]*. Alternatively, consider the use of non-opioid analgesics in these patients.

5.6 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.

5.7 Severe Hypotension

TALWIN 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 Drug Interactions (7)]*. Monitor these patients for signs of hypotension after initiating or titrating the dosage of TALWIN. In patients with circulatory shock, TALWIN may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of TALWIN in patients with circulatory shock.

5.8 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), TALWIN 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 TALWIN.

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

5.9 Risks of Use in Patients with Gastrointestinal Conditions

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

The pentazocine in TALWIN 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.

5.10 Increased Risk of Seizures in Patients with Convulsive or Seizure Disorders

The pentazocine in TALWIN 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 TALWIN therapy.

5.11 Withdrawal

The use of TALWIN, 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 TALWIN with a full opioid agonist analgesic.

When discontinuing TALWIN in a physically-dependent patient, gradually taper the dosage [*see Dosage and Administration (2.4)*]. Do not abruptly discontinue TALWIN in these patients *[see Drug Abuse and Dependence (9.3)]*.

5.12 Risks of Driving and Operating Machinery

TALWIN 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 TALWIN and know how they will react to the medication [see Patient Counseling Information (17)].

5.13 Tissue Damage at Injection Sites

Severe sclerosis of the skin, subcutaneous tissues, and underlying muscle have occurred at the injection sites of patients who have received multiple doses of pentazocine lactate. Constant rotation of injection sites is, therefore, essential. In addition, animal studies have demonstrated that TALWIN is tolerated less well subcutaneously than intramuscularly *[see Dosage and Administration (2.2)]*.

5.14 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. Data suggest that intravenous administration of pentazocine increases systemic and pulmonary arterial pressure and systemic vascular resistance in patients with acute myocardial infarction.

5.15 Impaired Renal or Hepatic Function

Although laboratory tests have not indicated that TALWIN 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.

5.16 Biliary Surgery

Narcotic drug products are generally considered to elevate biliary tract pressure for varying periods following their administration. Some 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.

5.17 Allergic-Type Reactions to Acetone Sodium Bisulfite

A sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people, is contained in multiple-dose vials. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people. The ampuls in the Uni-Amp™ Pak do not contain acetone sodium bisulfite.

6 ADVERSE REACTIONS

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

- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]*
- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.2)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.3)]*
- Interactions withBenzodiazepines or Other CNS Depressants *[see Warnings and Precautions (5.4)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.6)]*
- Severe Hypotension *[see Warnings and Precautions (5.7)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.9)]*
- Seizures *[see Warnings and Precautions (5.10)]*
- Withdrawal *[see Warnings and Precautions (5.11)]*

The following adverse reactions have been identified during post approval 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 TALWIN 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 with ingredients contained in TALWIN.

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids *[see Clinical Pharmacology (12.2)]*.

7 DRUG INTERACTIONS

Table 1 includes clinically significant drug interactions with TALWIN.

Table 1: Clinically Significant Drug Interactions with TALWIN

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 Warnings and Precautions (5.5)]*.
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 TALWIN 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 TALWIN 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 TALWIN 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 TALWIN is used concomitantly with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome. Available data with TALWIN 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 [see Data]. 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 [*see Warnings and Precautions (5.3)*].

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. TALWIN is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including TALWIN, 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 TALWIN during labor have experienced 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).

8.2 Lactation

Risk Summary

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TALWIN and any potential adverse effects on the breastfed infant from TALWIN or from the underlying maternal condition.

Clinical Considerations

Infants exposed to TALWIN 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.

8.3 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 Adverse Reactions (6.2)*].

8.4 Pediatric Use

The safety and efficacy of TALWIN as preoperative or preanesthetic medication have been established in pediatric patients 1 to 16 years of age. Use of TALWIN in these age groups is supported by evidence from adequate and controlled studies in adults with additional data from published controlled trials in pediatric patients. The safety and efficacy of TALWIN as a premedication for sedation have not been established in pediatric patients less than one year old. Information on the safety profile of TALWIN as a postoperative analgesic in children less than 16 years is limited.

8.5 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 occurred 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 TALWIN slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression *[see Warnings and Precautions (5.5)]*.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.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

TALWIN contains pentazocine, a Schedule IV controlled substance.

9.2 Abuse

TALWIN contains pentazocine, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone and

tapentadol. TALWIN can be abused and is subject to misuse, addiction, and criminal diversion [*see Warnings and Precautions (5.1)]*.

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.

TALWIN, 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 TALWIN Injection

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

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

9.3 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.

TALWIN should not be abruptly discontinued in a physically-dependent patient [*see Dosage and Administration (2.4)*]. If TALWIN 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 Use in Specific Populations (8.1)]*.

10 OVERDOSAGE

Clinical Presentation

Acute overdose with TALWIN 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 Clinical Pharmacology (12.2)]*.

Treatment of Overdose

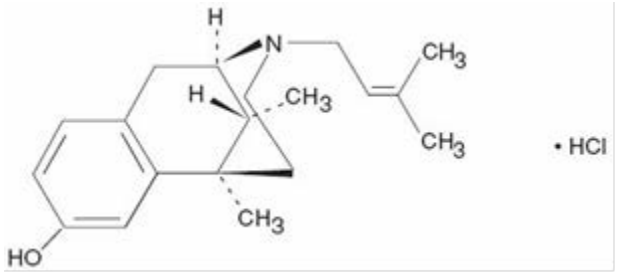
In case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac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

11 DESCRIPTION

TALWIN injection contains pentazocine lactate, a partial opioid agonist. Pentazocine is a member of the benzazocine series (also known as the benzomorphan series).

Chemically, pentazocine lactate is 1, 2, 3, 4, 5, 6-hexahydro-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocin-8-ol lactate, a white, crystalline substance soluble in acidic aqueous solutions, and has the following structural formula:



C19H27NO·HCl Molecular Weight: 321.88

12 CLINICAL PHARMACOLOGY

12.1 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.

12.2 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 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 Adverse Reactions (6.2)*].

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 [see Adverse Reactions (6.2)].

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 *[see Dosage and Administration (2.1, 2.X)]*.

Concentration–Efficacy Relationships

TALWIN 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 TALWIN to morphine ratio may range

from 20 mg to 40 mg TALWIN 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. TALWIN 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. TALWIN 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 Dosage and Administration (2.1)*]. 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 Dosage and Administration (2.1, 2.2)*].

12.3 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term animal studies to evaluate the carcinogenic potential of pentazocine have not been conducted.

Mutagenesis

Studies to evaluate the mutagenic potential of pentazocine have not been conducted.

Impairment of Fertility

Animal studies to evaluate the impact of pentazocine on fertility have not been conducted.

16 HOW SUPPLIED/STORAGE AND HANDLING

TALWIN (pentazocine) 30 mg/mL for injection is supplied as:

NDC Number	Container	Concentration	Fill	Quantity
0409-1920-10	Multiple-Dose Vial	30 mg/mL	10 mL	Box of 10
Each mL contains pentazocine lactate equivalent to 30 mg base and 2 mg acetone sodium bisulfite, 1.5 mg sodium chloride, and 1 mg methylparaben as preservative, in Water for Injection.				
0409-1941-01	Ampul	30 mg/mL	1 mL	Uni-Amp™ Pak of 25
Each mL contains pentazocine lactate equivalent to 30 mg base and 2.8 mg sodium chloride, in Water for Injection.				

The pH of TALWIN solutions is adjusted between 4 and 5 with lactic acid or sodium hydroxide. The air in the ampuls and vials has been displaced by nitrogen gas.

Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.]

17 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 Drug Interactions (7)*].

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention [*see Adverse Reactions (6), Clinical Pharmacology (12.2)*].

Hospira, Inc., Lake Forest, IL 60045 USA

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