1.3.1

Summary Of Product Characteristics (SPC)

1.3.1 Product information for health professionals

1.3.1.1 Invented Name of the Medicinal Product

G-PENT

Pentazocine Injection BP

1.3.1.2 Strength

Pentazocine 30 mg/ml

1.3.1.3 Pharmaceutical Form

Injection

1.3.1.4 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml Contains:

Pentazocine Lactate BP Eq. to Pentazocine ……30 mg

Sodium Chloride BP ……2.8 mg

Water for Injection BP…….……..q.s.

1.3.1.5 PHARMACEUTICAL FORM

Injection

A colourless to almost colourless solution.

1.3.1.6 CLINICAL PARTICULARS

1.3.1.6.1 Therapeutic indications

G-Pent is indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. **G-Pent** 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, reserves G-Pent 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

1.3.1.6.1 POSOLOGY AND METHOD OF ADMINISTRATION

Method of administration: Injectable

Posology:

Important Dosage and Administration Instructions:

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals.
- 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.
- Monitor patients closely for respiratory depression, especially within the first 24–72 hours of initiating therapy and following dosage increases with G-Pent and adjust the dosage accordingly.
- Do not mix G-Pent 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 G-Pent than younger patients. Elderly patients generally should be started on low doses of G-Pent and observed closely.

The subcutaneous route of administration should be used only when necessary because of possible severe tissue damage at injection sites. 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: G-Pent should not be mixed in the same syringe with soluble barbiturates because precipitation will occur.

Initiating Treatment with G-Pent

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

Titration and Maintenance of Therapy

Individually titrate G-Pent to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving G-Pent 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. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic titration.

If the level of pain increases after dosage stabilization, attempt to identify the source of increased pain before increasing the G-Pent 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 G-Pent

When a patient who has been taking G-Pent regularly and may be physically dependent no longer requires therapy with G-Pent, 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 G-Pent in a physically-dependent patient.

1.3.1.6.3 CONTRAINDICATIONS

G-Pent is contraindicated in patients with:

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

1.3.1.6.5 WARNING AND PRECAUTIONS

Addiction, Abuse, and Misuse

G-Pent contains pentazocine, a Schedule IV controlled substance.

As an opioid, G-Pent 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 G-Pent. 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 G-Pent, and monitor all patients receiving G-Pent 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 G-Pent, but use in such patients necessitates intensive counseling about the risks and proper use of G-Pent 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 G-Pent.

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. Carbon dioxide (CO2) 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 G-Pent, 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 G-Pent.

To reduce the risk of respiratory depression, proper dosing and titration of G-Pent are essential. Overestimating the G-Pent 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 G-Pent 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.

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

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

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 G-Pent 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.

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

The use of G-Pent 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: G-Pent 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 G-Pent.

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 G-Pent and when G-Pent 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

G-Pent 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).

Monitor these patients for signs of hypotension after initiating or titrating the dosage of G-Pent. In patients with circulatory shock, G-Pent may cause vasodilation that can further reduce cardiac output and blood pressure.

Avoid the use of G-Pent 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 CO2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), G-Pent may reduce respiratory drive, and the resultant CO2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with G-Pent.

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

Risks of Use in Patients with Gastrointestinal Conditions

G-Pent is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The pentazocine in G-Pent 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

The pentazocine in G-Pent 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 G-Pent therapy.

Withdrawal

The use of G-Pent, 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 G-Pent with a full opioid agonist analgesic.

When discontinuing G-Pent in a physically-dependent patient, gradually taper the dosage. Do not abruptly discontinue G-Pent in these patients.

Risks of Driving and Operating Machinery

G-Pent 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 G-Pent and know how they will react to the medication.

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 G-Pent is tolerated less well subcutaneously than bintramuscularly.

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.

Impaired Renal or Hepatic Function

Although laboratory tests have not indicated that G-Pent 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 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.

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.

1.3.1.6.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Table 1 includes clinically significant drug interactions with G-Pent.

Table 1: Clinically Significant Drug Interactions with G-Pent

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.
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 G-Pent 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 G-Pent 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 G-Pent 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 G-Pent is used concomitantly with anticholinergic drugs.

1.3.1.6.6 PREGNANCY AND LACTATION

Pregnancy

Risk Summary

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

In animal reproduction studies, pentazocine administered subcutaneously to pregnant hamsters during the early gestational period produced neural tube defects (i.e., exencephaly and cranioschisis) at 4.4 times the maximum daily dose. Based on animal data, advise pregnant women of the potential risk to a fetus. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly.

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. G-Pent is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic

techniques are more appropriate. Opioid analgesics, including G-Pent, 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 G-Pent during labor have experienced no adverse effects other than those that occur with commonly used analgesics.

Lactation

Risk Summary

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

Clinical Considerations

Infants exposed to G-Pent 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.

1.3.1.6.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

None.

1.3.1.6.8 UNDESIRABLE EFFECTS

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

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

- Seizures
- Withdrawal

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 G-Pent 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 G-Pent.

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids.

1.3.1.6.9 OVERDOSE

Clinical Presentation

Acute overdose with G-Pent 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.

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.

1.3.1.7 PHARMACOLOGICAL PROPERTIES

1.3.1.7.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opioid receptor agonist; analgesic.

ATC code: N02AD01

Mechanism of Action

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

Pharmacodynamics

Effects on the Central Nervous System

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

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

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Pentazocine causes a reduction 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.

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

Effects on the Immune System

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

Concentration–Efficacy Relationships

G-Pent 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 G-Pent to morphine ratio may range from 20 mg to 40 mg G-Pent 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. G-Pent weakly antagonizes the analgesic effects of morphine, meperidine, and phenazocine; in addition, it produces incomplete reversal of cardiovascular, respiratory, and behavioral depression by morphine and meperidine. G-Pent has about 1/50 the antagonistic activity of nalorphine. It also has sedative activity.

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. The minimum effective analgesic concentration of pentazocine for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance.

Concentration–Adverse Reaction Relationships

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

1.3.1.7.2 Pharmacokinetic properties

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.

1.3.1.7.3 Preclinical safety data

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.

1.3.1.8 PHARMACEUTICAL PARTICULARS

1.3.1.8.1 List of excipients

Lactic Acid
Sodium chloride
Water for Injection

1.3.1.8.2 Incompatibilities

Not applicable.

1.3.1.8.3 Shelf life

Three years.

1.3.1.8.4 Special precautions for storage

Store below 30°C. Protected from light.

1.3.1.8.5 Nature and contents of container

G-Pent (Pentazocine Injection BP) is filled in 1 ml clear glass ampoule. The 10 sealed ampoules are labeled and packed in a carton along with the package insert. (10 x 1).

1.3.1.8.6 Special precautions for disposal and other Special handling

None

1.3.1.9 Marketed by:

M/S. AQUATIX PHARMACEUTICALS LIMITED,
NO. 14, PRINCE BODE, OLUWO STREET, MENDE,
MARYLAND, LAGOS, NIGERIA.,