1.3 PRODUCT INFORMATION

1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

Name of Medicinal Product

Pentazocine Injection BP 30 mg/ml

1.1 Brand Name

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1.2 Strength of Medicinal Product

Each mL contains:

Pentazocine BP 30 mg

Excipients Q.S

Pharmaceutical Dosage form

Injection

2.0. Qualitative & Quantitative Composition

Each mL contains:

Pentazocine BP 30 mg

Excipients Q.S

Sr. No.	Raw Material	Specs	Quantity Mg/Ampoule.	Qty. for Std. Batch size 11 L (in kg)
1	Pentazocine	BP	30.00	0.330
2	Sodium Chloride	USP	2.8	0.0308
3	Lactic Acid	BP	0.011 ml	121 mL
4	Lactic Acid	BP	QS to adjust pH	QS to adjust pH
5	Water for Injection	BP	QS	1.500

3.0 Pharmaceutical Dosage form

Injection

4.1 Clinical Particulars

4.2 Therapeutic indications

Adults

Pentazocine is an anxiolytic, anticonvulsant and central muscle-relaxant. Pentazocine is used to relieve anxiety and provide sedation in severe acute anxiety or agitation and for the management of agitation associated with delirium tremens.

Pentazocine is used to relieve acute muscle spasm and tetanus.

Acute convulsions including status epilepticus, also convulsions due to poisoning and febrile convulsions. As an adjunct during endoscopy, in dentistry, surgery, radiology. Cardiac catheterisation, cardioversion, used pre-operatively to relieve anxiety, provide sedation, light anaesthesia and anterograde amnesia.

Paediatric patients

Pentazocine Injection BP is used:
• to treat status epilepticus, convulsions due to poisoning, and febrile convulsions;
• to treat tetanus;
• as a pre-operative medication or premedication.

The suitability of treatment with Pentazocine Injection BP in this population may need to be assessed on a case-by-case basis – see section 4.2.

General

Pentazocine Injection BP contains propylene glycol and ethanol. This should be taken into consideration when use of a parenteral benzodiazepine is indicated, especially when used in high volumes (e.g. continuous infusion of high doses to treat tetanus or status epilepticus) and/or when used in patients at risk of developing propylene glycol toxicity (see section 4.4).

4.3 Posology and method of administration:

Posology

Adults

Severe acute anxiety or agitation:

10 mg IV or IM injection which may be repeated after an interval of not less than

4 hours.

Delirium Tremens:

10 – 20 mg IV or IM.

Higher doses may be needed depending on the severity of symptoms.

Acute Muscle Spasm:

10 mg IV or IM injection which may be repeated after an interval of not less than 4 hours.

Tetanus:

Initially an IV dose of 0.1 - 0.3 mg/kg body weight, repeated at intervals of 1 - 4 hours.

Continuous IV infusion of 3 – 10 mg / kg body weight per 24 hours can also be used. The chosen dose should be related to the severity of the case and in extremely severe cases higher doses have been used.

Status epilepticus, convulsions due to poisoning:

10 – 20 mg IV or IM, repeated if necessary 30 - 60 minutes later.

If indicated, this may be followed by slow intravenous infusion (maximum dose 3 mg / kg body weight over 24 hours).

Pre-operative medication or premedication:

0.2 mg / kg body weight. The usual adult dose is 10 – 20 mg but higher doses may be necessary according to the clinical response.

Elderly or Debilitated Patients:

Doses should not exceed half those normally recommended.

Hepatic Impairment

In patients with chronic hepatic disease the dosage of Pentazocine Injection BP may need to be reduced. Medical monitoring is required in patients with impaired hepatic function when Pentazocine Injection BP is administered at doses of 0.45 mg / kg / day (equivalent to 50 mg / kg / day of propylene glycol) and above (see section 4.4).

Renal Impairment

In renal failure there is no clinically significant change to the half-life of Pentazocine and a dose adjustment is usually not necessary. Medical monitoring is required in patients with impaired renal function when Pentazocine Injection BP is administered at doses of 0.45 mg / kg / day (equivalent to 50 mg / kg / day of propylene glycol) and above (see section 4.4)

Cardiorespiratory Impairment

A lower dose is recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression.

Pediatric population

Pentazocine Injection BP contains propylene glycol and ethanol (see section 4.4). The European Medicines Agency (EMA) has recommended daily exposure limits for the excipient propylene glycol in the following paediatric populations:

Population	Recommended EMA propylene glycol exposure limit
Neonates	1 mg / kg / day propylene glycol (equivalent to administration of Pentazocine Injection BP at a dose of 9 micrograms / kg / day)
Infants and young children ≥ 1 month and < 5 years of age	50 mg / kg / day propylene glycol (equivalent to administration of Pentazocine Injection BP at a dose of 0.45 mg / kg / day)
Children ≥ 5 years old	500 mg / kg / day propylene glycol (equivalent to administration of Pentazocine Injection BP at a dose of 4.5 mg / kg / day)

Treatment with Pentazocine Injection BP at the doses recommended for paediatric patients in the indications below may correspond to a propylene glycol dose which may exceed the associated EMA exposure limit. In such a situation any decision to use Pentazocine Injection BP should be made on a case-by-case basis and following a careful assessment of the potential benefits and risks of treatment

Status epilepticus, convulsions due to poisoning, febrile convulsions:

By intravenous injection:

Paediatric population	Dosing recommendation
Neonates	300–400 micrograms / kg, then 300–400 micrograms / kg after 10 minutes if required. Each injection to be given over 3–5 minutes.
Children 1 month – 11 years	300–400 micrograms / kg (maximum per dose 10 mg), then a further 300–400 micrograms / kg injection after 10 minutes, if required. Each injection to be given over 3 – 5 minutes
Children 12 – 17 years	10 mg then a further 10 mg after 10 minutes, if required. Each injection to be given over 3 – 5 minutes.

Tetanus:

By intravenous injection:

• 100– 300 micrograms / kg every 1–4 hours.

By intravenous infusion:

• 3–10 mg / kg body weight, adjusted according to response, to be given over 24 hours.

Pre-operative medication or premedication:

0.2 mg / kg body weight. The injection should be given slowly (0.5 ml per minute).

Method of administration

Pentazocine Injection BP may be given IV injection, IM injection, or by IV infusion. The absorption from IM injection of Pentazocine may be variable, particularly for the gluteal muscles, and therefore the IM route of administration should only be used if IV administration is not possible.

Dilution

When administered via intravenous infusion, Pentazocine Injection BP should be diluted in either Glucose 5% or Sodium Chloride 0.9% to a concentration of no more than 80 micrograms Pentazocine / ml – see also section 6.2. Pentazocine Injection BP should not be diluted when administered via intravenous or intramuscular injection.

Intravenous use

IMPORTANT: In order to reduce the likelihood of adverse effects during intravenous administration the injection should be given slowly (1.0ml solution per minute). It is advisable to keep the patient supine for at least an hour after administration. Except in emergencies, a second person should always be present during intravenous use and facilities for resuscitation should always be available.

Intravenous injection may be associated with local reactions and thrombophlebitis and venous thrombosis may occur. In order to minimise the likelihood of these effects, intravenous injections of Pentazocine should be given into a large vein of the antecubital fossa.

Duration of treatment

The duration of treatment should be as short as possible in order to minimise the potential adverse effects of Pentazocine itself (e.g. the potential for dependence and associated withdrawal effects, the potential for interactions with other CNS depressants) as well as the potential for the development of adverse effects associated with product excipients propylene glycol and ethanol (see section 4.4). Pentazocine Injection BP is intended for short-term use to address an acute clinical need when parenteral Pentazocine is indicated. A transition from

parenteral to oral therapy, if required, should be made as soon as the clinical situation allows.

Medical monitoring

In general, it is recommended that patients should remain under medical supervision until at least one hour has elapsed from the time of injection / infusion. Patients should always be accompanied home by a responsible adult, with a warning not to drive or operate machinery for 24 hours.

Depending on the dose of Pentazocine Injection BP administered, further medical monitoring may be required in populations at risk of developing propylene glycol toxicity – see recommendations for use in patients with renal or hepatic impairment and for use in paediatric patients (Posology, above). See also section 4.4.

4.4 Contraindications

• Known hypersensitivity to diazepam, other benzodiazepines, propylene glycol or any of the other product excipients (see section 6.1).

• Phobic or obsessional states; chronic psychosis, hyperkinesis (paradoxical reactions may occur)

• Acute pulmonary insufficiency, respiratory depression, acute or chronic severe respiratory insufficiency (ventilator failure may be exacerbated).

• Sleep apnoea syndrome (condition may be exacerbated).

• Marked neuromuscular respiratory weakness including unstable myasthenia gravis (condition may be exacerbated).

• Severe hepatic impairment (elimination half-life of Pentazocine may be prolonged).

• Acute porphyria

• Planning a pregnancy (see section 4.6)

• Pregnancy (unless there are compelling reasons – see section 4.6)

Pentazocine Injection should not be used alone in the treatment of depression or anxiety associated with depression due to the risk of precipitation of suicide in this patient group.

Special warnings and precautions for use

Intramuscular administration

The IM use of Pentazocine injection can lead to a rise in serum creatinine phosphokinase activity, with a maximum level occurring between 12 and 24 hours after injection. This fact should be taken into account in the differential diagnosis of myocardial infarction.

Propylene glycol

Pentazocine Injection BP contains both propylene glycol (550 mg per ml) and ethanol (250 mg per ml) – see also Ethanol content, below. Various adverse events have been reported with high doses or prolonged use of propylene glycol, such as hyperosmolality, lactic acidosis; renal dysfunction (acute tubular necrosis), acute renal failure; cardiotoxicity (arrhythmia, hypotension); central nervous system disorders (depression, coma, seizures); respiratory depression, dyspnoea; liver dysfunction; haemolytic reaction (intravascular haemolysis) and haemoglobinuria; or multisystem organ dysfunction,. Adverse events usually reverse following weaning off of propylene glycol, and in more severe cases following hemodialysis.

Propylene glycol safety thresholds by population:

• Neonates

In neonates, a safety threshold of 1mg / kg / day has been set for excipient propylene glycol by the European Medicines Agency (corresponding to a 9 microgram / kg / day dose of Pentazocine Injection BP) Exceeding this threshold may induce serious adverse effects in this population when co-administered with any substrate for alcohol dehydrogenase (such as ethanol).

• Infants and children younger than 5 years old

In infants and children younger than 5 years old, a safety threshold of 50 mg / kg / day has been set for excipient propylene glycol by the European Medicines Agency (corresponding to a 0.45 mg / kg /day dose of Pentazocine Injection BP). The co-administration of propylene glycol at or above this safety threshold with any substrate for alcohol dehydrogenase (such as ethanol) may induce adverse effects in this population.

• Adults and children aged 5 years and older

In adults and children aged 5 years and older a safety threshold of 50 mg / kg / day has been set for excipient propylene glycol by the European Medicines Agency (corresponding to a 4.5 mg / kg /day dose of Pentazocine Injection BP).

• Patients with hepatic or renal impairment

Various adverse events attributable to propylene glycol have been reported such as renal dysfunction (acute tubular necrosis), acute renal failure, and liver

dysfunction. A safety threshold of 50 mg / kg / day propylene glycol (equivalent to 0.45 mg / kg / day Pentazocine Injection BP) has therefore been set by the EMA in patients with compromised hepatic or renal function.

Any decision to use Pentazocine Injection BP at doses which would exceed the corresponding EMA exposure limit for propylene glycol should be made on a case-by-case basis and following a careful assessment of the potential benefits and risks of treatment. Medical monitoring is required should treatment be considered appropriate.

The additive effect of treatment with Pentazocine Injection BP with other products containing propylene glycol and/or any substrate for alcohol dehydrogenase and/or any dietary intake of these excipients should be taken into account.

Ethanol content

Co-administration with medicines containing e.g. propylene glycol or ethanol may lead to accumulation of ethanol and induce adverse effects, in particular in young children with low or immature metabolic capacity – see section 4.3 and Propylene glycol toxicity, above.

A single dose of 20 mg (i.e. two ampoules) of this medicine administered to an adult weighing 70 kg would result in exposure to 14 mg/kg of ethanol which may cause a rise in blood alcohol concentration (BAC) of about 2.4 mg/100 ml.

For comparison, for an adult drinking a glass of wine or 500 ml of beer, the BAC is likely to be about 50 mg/100 ml.

Pentazocine Injection BP may also be given by continuous intravenous infusion. IV infusion of the maximum recommended dose of 10 mg / kg body weight / 24 hours to treat tetanus in an adult patient weighing 70 kg would result in 700 mg (i.e. 70 ampoules) of this medicine being given in a 24-hour period. This would theoretically result in exposure to 500 mg/kg of ethanol which may cause a rise in blood alcohol concentration (BAC) of about 83 mg/100 ml. Given the slow administration as an infusion within the 24-hour period, the effects of alcohol may be reduced.

The additive effect of treatment with Pentazocine Injection BP with other ethanol-containing products and/or any dietary intake of ethanol should be taken into account.

Risk from concomitant use of opioids

Concomitant use of Pentazocine and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs such as Pentazocine with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Pentazocine concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers (where applicable) to be aware of these symptoms (see section 4.5).

Concomitant use of alcohol/ other CNS depressants

The concomitant use of Pentazocine with alcohol and/or CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of Pentazocine possibly including severe sedation, clinically relevant respiratory and/or cardio-vascular depression (see section 4.5).

Tolerance

Loss of efficacy effects may develop after repeated use for a few weeks. Limits of tolerance in patients with organic cerebral changes (particularly arteriosclerosis) or cardiorespiratory insufficiency may be very wide (see also section 4.3); care must be taken in adapting the dosage with such patients.

Dependence

The risk of dependence (physical or psychological) increases with dose and duration of treatment and is greater in patients with a history of alcohol or drug abuse, or in patients with a marked personality disorder. Therefore

• regular monitoring of such patients is essential

• routine repeat use should be avoided

• treatment should be withdrawn gradually

Abuse of Pentazocine has been reported.

Withdrawal effects

The duration of treatment should be as short as possible (see section 4.2).

If physical dependence has developed, abrupt termination of treatment results in withdrawal symptoms. These include headache, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability, sleep disturbance, diarrhoea and mood changes. In severe cases the following may occur: a feeling of unreality or of being separated from the body, derealisation, depersonalisation, confusional states, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, psychotic manifestations including hallucinations or epileptic seizures. Withdrawal symptoms will be worse in patients who have been dependent on alcohol or other narcotic drugs in the past, but can occur following abrupt cessation of treatment in patients receiving normal therapeutic doses for a short period of time.

Rebound insomnia and anxiety

A transient syndrome whereby the symptoms that led to treatment with a benzodiazepine recur in an enhanced form, may occur on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety or sleep disturbances and restlessness. Since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually.

Sudden discontinuation of treatment with Pentazocine in patients with epilepsy or other patients who have had a history of seizures can result in convulsions or epileptic status. Convulsions can also be seen following sudden discontinuation in individuals with alcohol or drug abuse.

Discontinuation should be gradual in order to minimise the risk of withdrawal symptoms.

Duration of treatment

The duration of treatment should be as short as possible (see section 4.2) depending on the indication. The patient must be evaluated after a period of no more than 4 weeks and then regularly thereafter in order to assess the need for continued treatment, especially if the patient is free of symptoms. In general, treatment must not last any longer than 8-12 weeks, including the tapering off process. Extension beyond these periods should not take place without re-evaluation of the situation.

It may be useful to inform the patient when treatment is started that it will be of limited duration and to explain precisely how the dosage will be progressively decreased. Moreover it is important that the patient should be aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms should they occur while the medicinal product is being discontinued. There are indications that, in the case of benzodiazepines with a short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high.

When benzodiazepines with a long duration of action are being used it is important to warn against changing to a benzodiazepine with a short duration of action, as withdrawal symptoms may develop.

Amnesia

Anterograde amnesia may occur even if benzodiazepines are used within the normal dose range, though this is seen in particular at high dose levels. The condition occurs most often several hours after ingesting the product and therefore to reduce the risk patients should ensure that they will be able to have an uninterrupted sleep of 7–8 hours (see also section 4.8). Amnestic effects may be associated with inappropriate behaviour.

Bereavement/ loss

Psychological adjustment may be inhibited by benzodiazepines.

Psychiatric and 'paradoxical' reactions

Reactions such as restlessness, agitation, irritability, aggressiveness, excitement, confusion, delusions, rage, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects can occur.

These reactions are more likely in children and the elderly, and extreme caution should be used in prescribing benzodiazepines to patients with personality disorders. Should they occur, treatment should be discontinued.

Specific Patient Groups

Patients with depression

Pentazocine should not be used alone to treat depression or anxiety associated with depression as suicide may be precipitated in such patients.

Patients with a history of alcohol & drug abuse, and patients on disulfiram

Pentazocine should be used with extreme caution in patients with a history of alcohol or drug abuse (risk of abuse/dependence) – see Propylene glycol toxicity and Ethanol content, above. Pentazocine should not be used concomitantly with disulfiram due to its ethanol content. A reaction may occur as long as two weeks after cessation of disulfiram (see section 4.5).

Patients with phobias and/or chronic psychoses

Pentazocine is not recommended (inadequate evidence of efficacy and safety)

Potentially suicidal patients

Potentially suicidal individuals should not have access to large amounts of Pentazocine due to the risk of overdosing

Psychotic illness

Benzodiazepines are not recommended for the primary treatment of psychotic illness.

Paediatric population

Benzodiazepines should not be given to children without careful assessment of the need to do so; the duration of treatment must be kept to a minimum. Owing to the propylene glycol and ethanol content of Pentazocine Injection BP, treatment at doses recommended of Pentazocine for paediatric patients may correspond to a propylene glycol dose which may exceed the associated EMA exposure limit. In such a situation any decision to use Pentazocine Injection BP should be made on a case-by-case basis and following a careful assessment of the potential benefits and risks of treatment (see section 4.2 and Propylene glycol toxicity and Ethanol content, above).

Elderly and debilitated patients

Elderly and debilitated patients should be given a reduced dose (see section 4.2). Due to the myorelaxant effect there is a risk of falls and consequently hip fractures in the elderly.

Hepatic Impairment

Benzodiazepines are not indicated to treat patients with severe hepatic insufficiency as they may precipitate encephalopathy. In patients with chronic hepatic disease dosage may need to be reduced. Medical monitoring in patients with impaired hepatic function may be required (see section 4.2 and Propylene glycol toxicity,

above).

Renal Impairment

The usual precautions in treating patients with impaired renal function should be observed. In renal failure, the half-life of Pentazocine is not clinically significantly changed, and dose adjustment is usually not necessary. Medical monitoring in patients with impaired renal function may be required (see section 4.2 and Propylene glycol toxicity, above).

Cardiorespiratory Impairment

A lower dose is recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression (see section 4.2).

Pentazocine injection should be administered with caution to patients in whom a drop in blood pressure might lead to cardiovascular or cerebrovascular complications.

Sodium content

This medicine contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction
Particular attention should be paid to the potential effects of drug interactions with Pentazocine in the elderly.

Opioids

The concomitant use of sedative medicines such as benzodiazepines or related drugs such as Pentazocine with opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited (see section 4.4).

Not recommended

Alcohol

Pentazocine should not be used together with alcohol (CNS inhibition enhanced sedative effects: impaired ability to drive/ operate machinery).

Sodium oxybate

Avoid concomitant use (enhanced effects of sodium oxybate)

HIV-protease inhibitors

Avoid concomitant use (increased risk of prolonged sedation) – see below for zidovudine.

Take into account

Pharmacodynamic interactions

If Pentazocine is used with other centrally acting agents, careful consideration has to be given to the pharmacology of the agents employed, particularly with compounds that may potentiate or be potentiated by the action of diazepam, such as neuroleptics, anxiolytics/sedatives, hypnotics, antidepressants, anticonvulsants, sedating antihistamines, antipsychotics, anaesthetics for general anaesthesia and narcotic analgesics. Such concomitant use may increase sedative effects and cause depression of respiratory and cardiovascular functions. Concomitant use of narcotic analgesics may promote psychological dependency due to enhancement of euphorigenic effects.

Anti-epileptic drugs

Pharmacokinetic studies on potential interactions between Pentazocine and antiepileptic drugs have produced conflicting results. Both depression and elevation of drug levels, as well as no change, have been reported.

Phenobarbital taken concomitantly may result in an additive CNS effect. Increased risk of sedation and respiratory depression. Phenobarbital is a known inducer of CYP3A4 and increases hepatic metabolism of diazepam. Reduced effect of diazepam.

Special care should be taken in adjusting the dose in the initial stages of treatment.

Side effects may be more evident with hydantoins or barbiturates.

Pentazocine has been reported to be displaced from protein-binding sites by sodium valproate (increased serum levels: increased risk of drowsiness).

Narcotic analgesics

Enhancement of the euphoria may lead to increased psychological dependence.

Other drugs enhancing the sedative effect of diazepam

Cisapride, lofexidine, nabilone, disulfiram and the muscle-relaxants – baclofen, Tizanidine, suxamethonium and tubocurarine.

Compounds that affect hepatic enzymes (particularly cytochrome P450):

• Inhibitors (eg cimetidine: isoniazid: erythromycin: omeprazole: esomeprazole) reduce clearance and may potentiate the action of benzodiazepines.

Itraconazole, ketoconazole, and to a lesser extent fluconazole and voriconazole are potent inhibitors of the cytochrome P450 isoenzyme CYP3A4 and may increase plasma levels of benzodiazepines. The effects of benzodiazepines may be increased and prolonged by concomitant use. A dose reduction of the benzodiazepine may be required.

Rifamycins (rifampicin)

Rifampicin is a potent inducer of CYP3A4 and substantially increases the hepatic metabolism and clearance of diazepam. In a study with healthy subjects administered 600 mg or 1.2 g rifampicin daily for 7 days, the clearance of Pentazocine was increased by about fourfold. Co-administration with rifampicin gives rise to substantially decreased concentrations of diazepam. Reduced effect of diazepam. The concomitant use of rifampicin and Pentazocine should be avoided.

Antihypertensives, vasodilators & diuretics

Enhanced hypotensive effect with ACE inhibitors, alpha-blockers, angiotensin–II receptor antagonists, calcium channel blockers adrenergic neurone blockers, beta-blockers, moxonidine, nitrates, hydralazine, minoxidil, sodium nitroprusside and diuretics.

Enhanced sedative effect with alpha-blockers or moxonidine

Dopaminergics

Possible antagonism of the effect of levodopa

Antiviral agents (atazanavir, ritonavir, delavirdine, efavirenz, indinavir, nelfinavir, saquinavir)

Antiviral agents may inhibit the CYP3A4 metabolic pathway for diazepam. Increased risk of sedation and respiratory depression. Therefore, concomitant use should be avoided.

Zidovudine

Increased zidovudine clearance by diazepam

Oral contraceptives

Inhibition of oxidative metabolism of diazepam. Increased effects of diazepam.

Co-administration of Pentazocine and combined oral contraceptives has been known to cause breakthrough bleeding. The mechanism of this reaction is unknown. Breakthrough bleeding, but no contraceptive failures have been reported.

Theophylline

A proposed mechanism is competitive binding of theophylline to adenosine receptors in the brain. Counteraction of the pharmacodynamic effects of diazepam, e.g. reduction of sedation and psychomotor effects.

Caffeine

Concurrent use may result in reduced sedative and anxiolytic effects of diazepam.

Grapefruit juice

Inhibition of CYP3A4 may increase the plasma concentration of Pentazocine (possible increased sedation and amnesia). Cmax is increased by 1.5 times and AUC by 3.2 times. Possible increased effect of diazepam.

This interaction may have little significance in healthy individuals, but it is not clear is if other factors such as old age or liver cirrhosis increase the risk of adverse effects with concurrent use.

Antipsychotics

Plasma concentrations of zotepine may be increased. Severe hypotension, collapse, loss of consciousness, respiratory depression, and potentially fatal respiratory arrest have been reported in a few patients taking benzodiazepines and clozapine. Salivary hypersecretion has also occurred. Caution is advised when initiating clozapine therapy in patients taking diazepam. There is an increased risk of hypotension, bradycardia and respiratory depression when parenteral benzodiazepines are given with intramuscular olanzapine.

Pharmacokinetic interactions

Pentazocine is mainly metabolised to the pharmacologically active metabolites N-desmethyldiazepam, temazepam and oxazepam. The oxidative metabolism of Pentazocine is mediated by CYP3A4 and CYP2C19 isoenzymes. Oxazepam and temazepam are further conjugated to glucuronic acid. Inhibitors of CYP3A4 and/or CYP2C19 can give rise to increased concentrations of Pentazocine while enzyme inducing drugs such as rifampicin, hypericum perforatum and certain antiepileptics can result in substantially decreased plasma concentrations of diazepam.

Carbamazepine

Carbamazepine is a known inducer of CYP3A4 and increases hepatic metabolism of diazepam. This can result in up to three-fold greater plasma clearance and a shorter half-life of diazepam. Reduced effect of diazepam.

Phenytoin

Phenytoin is a known inducer of CYP3A4 and increases hepatic metabolism of diazepam. Reduced effect of diazepam.

The metabolism of phenytoin may be increased or decreased or remain unaltered by Pentazocine in an unpredictable way. Increased or decreased serum concentration of phenytoin. Phenytoin concentrations should be monitored more closely when Pentazocine is added or discontinued.

Azoles (fluconazole, itraconazole, ketoconazole, voriconazole)

Increased plasma concentration of benzodiazepines, due to inhibition of the CYP3A4 and/or CYP2C19 metabolic pathway.

Fluconazole: Co-administration with 400 mg fluconazole on the first day and 200 mg on the second day increased the AUC of a single 5 mg oral dose of Pentazocine 2.5-fold and prolonged the half-life from 31 hours to 73 hours.

Voriconazole: A study with healthy subjects found that 400 mg voriconazole twice daily on the first day and 200 mg twice daily on the second day increased the AUC of a single 5 mg oral dose of Pentazocine 2.2-fold and prolonged the half-life from 31 hours to 61 hours.

Increased risk of undesired effects and toxicity of benzodiazepine. Concomitant use should be avoided or the dose of Pentazocine reduced.

Fluvoxamine

Fluvoxamine inhibits both CYP3A4 and CYP2C19 which leads to inhibition of the oxidative metabolism of diazepam. Co-administration with fluvoxamine results in an increased half-life and an approximately 190% increased plasma concentrations (AUC) of diazepam. Drowsiness, reduced psychomotor performance and memory impairment may result. Preferably, benzodiazepines that are metabolised via a non-oxidative pathway should be used instead.

Corticosteroids

Chronic use of corticosteroids may cause increased metabolism of Pentazocine due to induction of cytochrome P450 isoenzyme CYP3A4, or of enzymes responsible for glucuronidation. Reduced effects of diazepam.

Cimetidine

Cimetidine inhibits the hepatic metabolism of diazepam, reducing its clearance and prolonging its half-life. In one study where 300 mg cimetidine was administered four times daily for 2 weeks, the combined plasma level of Pentazocine and its active metabolite, desmethyldiazepam, was found to be increased by 57%, but reaction times and other motor and intellectual tests remained unaffected. Increased action of Pentazocine and increased risk of drowsiness. Reduction of the Pentazocine dose may be necessary.

Omeprazole

Omeprazole inhibits the CYP2C19 metabolic pathway for diazepam. Omeprazole prolongs the elimination half-life of Pentazocine and increases the plasma concentrations (AUC) of Pentazocine approximately between 30% - 120%. The effect is seen in CYP2C19 extensive metabolisers but not in slow metabolisers, with a low clearance of diazepam. Increased action of diazepam. Reduction of the Pentazocine dose may be necessary.

Esomeprazole

Esomeprazole inhibits the CYP2C19 metabolic pathway for diazepam. Co-administration with esomeprazole results in an extended half-life and an increase in plasma concentrations (AUC) of Pentazocine by approximately 80%. Increased effect of diazepam. Reduction of the Pentazocine dose may be necessary.

Isoniazid

Isoniazid inhibits the CYP2C19 and CYP3A4 metabolic pathway for diazepam. Co-administration with 90 mg isoniazid twice daily for 3 days resulted in a prolonged elimination half-life of Pentazocine and in a 35% increased plasma concentration (AUC) of diazepam. Increased effect of diazepam.

Itraconazole

Increased plasma concentration of Pentazocine due to inhibition of the CYP3A4 metabolic pathway. In a study with healthy subject given 200 mg itraconazole daily for 4 days increased the AUC of a single 5 mg oral dose of Pentazocine by about 15%, but there was no clinically significant interaction as determined by psychomotor performance tests. Possible increased effect of diazepam.

Fluoxetine

Fluoxetine inhibits the metabolism of Pentazocine via CYP2C19 and other pathways, resulting in elevated plasma concentrations and decreased clearance of diazepam. Increased effect of diazepam. Concomitant use should be monitored closely.

Disulfiram

Reduced metabolism of Pentazocine leading to prolonged half-life and increased plasma concentration of diazepam. The elimination of the N-desmethyl metabolites of Pentazocine is slowed down which can give rise to marked sedative effects. Increased risk of CNS inhibition such as sedation.

Cisapride

Accelerated absorption of diazepam. Temporary increase of the sedative effects of orally administered diazepam.

Levodopa

Concomitant use with Pentazocine resulted in reduced effects of levodopa in a small number of case reports.

Ketamine

Due to similar oxidative processes, Pentazocine competitively inhibits ketamine metabolism. Pre-medication with Pentazocine leads to prolonged half-life of ketamine with enhanced effect as a result. Increased sedation.

4.6 Fertility, pregnancy and lactation

Pregnancy:

There is no evidence regarding the safety of Pentazocine in human pregnancy, nor is there evidence from animal studies, that it is free from hazard.

Pentazocine Injection BP contains propylene glycol (see sections 2 and 4.4). Although propylene glycol has not been shown to cause reproductive or

developmental toxicity in animals or humans, it may reach the foetus. Pentazocine Injection BP should not be used during pregnancy, especially during the first and last trimesters unless there are compelling reasons.

If Pentazocine is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuance of Pentazocine if she intends to become, or suspects that she is pregnant.

Results of retrospective studies suggest an increased risk of congenital malformation in infants or mothers who received Pentazocine during the first trimester of pregnancy.

Infants born to mothers who take benzodiazepines chronically during the later stages of pregnancy may develop physical dependence and may be at some risk for developing withdrawal symptoms in the postnatal period.

An increase in foetal heart rate has occurred after Pentazocine use during labour. Hypoactivity, hypotonia, hypothermia, apnoea, feeding problems, hyperbilirubinaemia and kernicterus have been reported in neonates born to mothers who receive large doses of Pentazocine (generally greater than 30 mg) shortly before delivery.

Breast-feeding:

Pentazocine has been detected in breast milk. Pentazocine Injection BP contains propylene glycol (see sections 2 and 4.4) which has also been found in breast milk.. Administration of Pentazocine Injection BP to lactating patients should be considered on a case-by-case basis.

Fertility:

Studies in animals have shown a decrease in pregnancy rate and reduced number of surviving offspring in rats at high doses. There are no human data.

4.7 Effects on ability to drive and use machines

Sedation, amnesia and impaired muscular function may adversely affect the ability to drive or use machines. If insufficient sleep occurs, the likelihood of impaired alertness may be increased (See also section 4.5). Patients should be warned that effects on the central nervous system may persist into the day after administration even after a single dose.

4.8 Undesirable effects

Drowsiness, numbed emotions, reduced alertness, confusion, fatigue, headache, dizziness, muscle weakness, ataxia or double vision predominantly occur at the start of therapy but usually disappear with repeated administration. Among elderly patients there may be confusion conditions at high dose levels. There is an increased risk of falls and associated fractures in elderly patients using benzodiazepines.

Increased salivary and bronchial secretion has been reported, in particular in children.

Amnesia

Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour (see section 4.4).

Dependence

Chronic use (even at therapeutic doses) may lead to the development of physical and psychological dependence: discontinuation of the therapy may result in withdrawal or rebound phenomena (see section 4.4). Abuse of benzodiazepines has been reported.

The frequencies of adverse events are ranked according to the following:

Very common (≥1/10)

Common (≥1/100 to <1/10)

Uncommon (≥1/1,000 to <1/100)

Rare (≥1/10,000 to <1/1,000)

Very rare (<1/10,000)

Not known (cannot be estimated from the available data).

System Organ Class	**Frequency**	**Undesirable effects**
Blood and lymphatic system disorders	Rare	Blood dyscrasias
	Very rare	Leukopenia, Thrombocytopenia, Agranulocytosis
Immune system disorders	Very rare	Hypersensitivity reactions, including anaphylaxis.
Metabolism and nutrition disorders	Not known	Metabolic disorders including metabolic acidosis, increased anion gap and hyperosmolality have been reported as a consequence of propylene glycol toxicity (see section 4.4 Special warnings and precautions for use).
Psychiatric disorders	Common	Confusion.
	Rare	Psychiatric and paradoxical reactions such as excitation, restlessness, agitation, irritability, aggressiveness, delusion, rages, hallucinations, psychoses, memory loss, nightmares, inappropriate behaviour and other adverse behavioural effects.[a] Emotional poverty, decreased alertness and depression.[b]
Nervous system disorders	Very common	Drowsiness.
	Common	Ataxia, impaired motor ability, tremor.
	Uncommon	Anterograde amnesia.[c] Concentration difficulties, balance disorders, dizziness, headache, slurred speech.

	Rare	Unconsciousness, insomnia, dysarthria.
Eye disorders	Not known	Reversible disorders of vision: blurred vision, diplopia, nystagmus.
Ear and labyrinth disorders	Not known	Vertigo
Cardiac disorders	Rare	Bradycardia, heart failure including cardiac arrest.
Vascular disorders	Rare	Hypotension, syncope. The incidence of hypotension may be reduced by not exceeding the recommended rate of administration. Patients should be managed in the supine position and kept there throughout the procedure.
	Not known	Intravenous injections of Pentazocine may be associated with local reactions and thrombophlebitis and venous thrombosis may occur.
Respiratory, thoracic and mediastinal disorders	Uncommon	Respiratory depression.
	Rare	Respiratory arrest, increased bronchial secretion.
	Not Known	Apnoea, worsening of obstructive pulmonary disease
Gastrointestinal disorders	Uncommon	Gastrointestinal disorders (nausea, vomiting, constipation, diarrhoea), increased salivary secretion.
	Rare	Dry mouth, increased appetite.
Hepatobiliary disorders	Rare	Jaundice, changes of hepatic parameters (elevation of ALT, AST, alkaline phosphatase).
Skin and subcutaneous tissue disorders	Uncommon	Allergic skin reactions (itching, erythema, rash).
Musculoskeletal and connective tissue disorders	Uncommon	Myasthenia.
Renal and urinary disorders	Rare	Urinary retention, incontinence.
Reproductive system and breast disorders	Rare	Gynaecomastia, impotence, increased or reduced libido.
General disorders and administration site conditions	Common	Fatigue, withdrawal symptoms (anxiety, panic, palpitations, sweating, tremor, gastrointestinal disorders,

		irritability, aggression, disrupted sensory perception, muscle spasms, general malaise, loss of appetite, paranoid psychosis, delirium, epileptic attacks, headache, muscle pain, depression, insomnia, restlessness, confusion and the occurrence of rebound phenomena).[d]
	Not known	Anaphylaxis, injection site pain or irritation (see also Vascular disorders)
Investigations	Very rare	Elevation of transaminases.

[a] Known to occur when using benzodiazepines or benzodiazepine-like agents. These reactions may be quite severe. They are more likely to occur in children and the elderly. Pentazocine should be discontinued if such symptoms occur (see section 4.4).

[b] Pre-existing depression may be unmasked during benzodiazepine use.

[c] May occur using therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour (see section 4.4).

[d] The likelihood and degree of severity of withdrawal symptoms is dependent on the duration of treatment, dose level and degree of dependency. In severe cases the following symptoms may occur: derealisation, depersonalisation, tinnitus, numbness and tingling of the extremities, hypersensitivity to light, noise, and physical contact, involuntary movements, hyperreflexia, tremor, nausea, vomiting, diarrhoea, abdominal cramps, loss of appetite, agitation, palpitations, tachycardia, panic attacks, vertigo, short-term memory loss, hallucinations/delirium, catatonia, hyperthermia, convulsions. Convulsions may be more common in patients with pre-existing seizure disorders, or those taking other drugs that lower the convulsive threshold such as antidepressants.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reactions via the MHRA website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose
Features

The symptoms of Pentazocine overdose are mainly an intensification of the therapeutic effects (ataxia, drowsiness, dysarthria, sedation, muscle weakness, profound sleep, hypotension, bradycardia, nystagmus) or paradoxical excitation. In most cases only observation of vital functions is required.

Extreme overdosage may lead to coma, areflexia, cardiorespiratory depression and apnoea, requiring appropriate countermeasures (ventilation, cardiovascular support). Benzodiazepine respiratory depressant effects are more serious in patients with severe chronic obstructive airways disease. Severe effects in overdose also include rhabdomyolysis and hypothermia.

Rarely, propylene glycol toxicity has been reported following higher than recommended doses (see section 4.4 Special warnings and precautions for use).

Management

Maintain a clear airway and adequate ventilation.

Monitor level of consciousness, respiratory rate, pulse oximetry and blood pressure in symptomatic patients.

Consider arterial blood gas analysis in patients who have a reduced level of consciousness (GCS < 8; AVPU scale P or U) or have reduced oxygen saturations on pulse oximetry.

Correct hypotension by raising the foot of the bed and by giving an appropriate fluid challenge. Where hypotension is thought mainly due to decreased systemic vascular resistance, drugs with alpha-adrenergic activity such as noradrenaline or high dose dopamine (10-30 micrograms/kg/min) may be beneficial. The dose of inotrope should be titrated against blood pressure.

If severe hypotension persists despite the above measures, then central venous pressure monitoring should be considered.

Supportive measures are indicated depending on the patient's clinical state.

Benzodiazepines are poorly dialysable.

Flumazenil, a benzodiazepine antagonist, is not advised as a routine diagnostic test in patients with reduced conscious level. It may sometimes be used as an alternative to ventilation in children who are naive to benzodiazepines, or in patients with COPD to avoid the need for ventilation. It is not necessary or appropriate in cases of poisoning to fully reverse the benzodiazepine effect. Flumazenil has a short half-life (about an hour) and in this situation an infusion may therefore be required. Flumazenil is contraindicated when patients have ingested multiple medicines, especially after co-ingestion of a benzodiazepine and a tricyclic antidepressant or any other drug that causes seizures. This is because the benzodiazepine may

suppress seizures induced by the second drug; its antagonism by flumazenil can reveal severe status epilepticus that is very difficult to control.

The use of flumazenil is not recommended in epileptic patients who have been receiving benzodiazepine treatment for a prolonged period. Although flumazenil exerts a slight intrinsic anticonvulsant effect, the abrupt suppression of the protective effect of a benzodiazepine agonist can give rise to convulsions in epileptic patients.

Contraindications to the use of flumazenil include features suggestive of a tricyclic antidepressant ingestion including a wide QRS, or large pupils. Use in patients postcardiac arrest is also contraindicated.

It should be used with caution in patients with a history of seizures, head injury, or chronic benzodiazepine use.

Occasionally a respirator may be required but generally few problems are encountered, although behavioral changes are likely in children.

If excitation occurs, barbiturates should not be used.

Effects of overdose are more severe when taken with centrally-acting drugs, especially alcohol, and in the absence of supportive measures, may prove fatal.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pentazocine is a benzodiazepine tranquilliser with anticonvulsant, sedative, muscle relaxant and amnesic properties. It is used in the treatment of anxiety and tension states, as a sedative and pre-medicant, in the control of muscle spasm as in tetanus, and in the management of alcohol withdrawal symptoms. It is of value in patients undergoing orthopaedic procedures endoscopy and cardioversion.

5.2 Pharmacokinetic properties

Pentazocine is metabolised to two active metabolites, one of which, desmethyldiazepam, has an extended half-life. Pentazocine is therefore a long acting benzodiazepine and repeated doses may lead to accumulation.

Pentazocine is metabolised in the liver and excreted via the kidney. Impaired hepatic or renal function may prolong the duration of action of diazepam. It is recommended that elderly and debilitated patients receive initially one half the normal recommended dose.

During prolonged administration, for example in the treatment of tetanus, the dosage should generally be reduced after 6-7 days, to reduce the likelihood of accumulation and prolonged CNS depression.

5.3 Preclinical safety data

No further information other than that which is included in the Summary of Product Characteristics.

6. Pharmaceutical particulars

6.1 List of excipients

Ethanol

Propylene Glycol

Sodium Hydroxide

Water for Injections

6.2 Incompatibilities
Pentazocine injection should not be mixed with other drugs or IV fluids and should not normally be diluted except when given slowly in large intravenous infusions of normal saline or dextrose. Not more than 40 mg of Pentazocine Injection BP should be added to a 500 ml infusion solution (i.e. a maximum concentration of 80 micrograms Pentazocine /ml). The solution should be freshly made up and used within six hours.

6.3 Shelf life
36 months

6.4 Special precautions for storage
Do not store above 25°C.

Keep container in the outer carton in order to protect from light.

6.5 Nature and contents of container
Type I clear glass ampoule, 2 ml. Packed in cardboard cartons to contain 10 ampoules x 2 ml.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder
Globezza International Ltd.
No. 4 & 6, Oyinlola street, by Pab Bus Stop, Council Ikotun Road,
Ikotun, Lagos, Nigeria

8. Marketing authorisation number(s)
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9. Date of first authorisation/renewal of the authorisation
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10. Date of revision of the text
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