SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

BUFYL 1.25 mg/ml and 2 micrograms/ml Solution for Infusion
Bupivacaine Hydrochloride 1.25 mg/ml and Fentanyl Citrate 2 micrograms/ml Solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of solution contains 1.25 mg bupivacaine hydrochloride and 2 micrograms of fentanyl (as fentanyl citrate)

Each 250 ml bag contains 312.5 mg of bupivacaine and 0.5 mg of fentanyl (as fentanyl citrate)

Each 500 ml bag contains 625 mg of bupivacaine and 1 mg of fentanyl (as fentanyl citrate)

Excipients with known effect
Each millilitre (ml) contains 3.45 mg of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.
Clear, colourless aqueous sterile solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Bufyl/ Bupivacaine and Fentanyl solution for infusion is indicated for:
(i) maintaining analgesia post-operatively and
(ii) for maintaining epidural analgesia during labour.

4.2 Posology and method of administration

Posology
Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with fentanyl in order to minimise

the risk of addiction and drug withdrawal syndrome (see section 4.4).

Adults
The length of continuous epidural infusions given post-operatively should be minimized, due to the increased risks of reaching a toxic plasma concentration, inducing local neural injury or local infection. Administration of bupivacaine with fentanyl epidural infusion has not been adequately studied for more than 72 hours.

The dosages in the following table are recommended as a guide for use in healthy adults during labour and in the post operative period. It should not be necessary to exceed an infusion dosage of 20 mg/hour for bupivacaine. Standard textbooks should be consulted for factors affecting specific block techniques; dosing should be titrated to meet the individual patient requirements and the lowest dose required to provide adequate analgesia should be used.

Table 1 - Recommended dosages for adults of Bufyl/ Bupivacaine 1.25 mg/ml and Fentanyl 2 micrograms/ml solution for infusion

Indication	**Administration by continuous epidural infusion**	**Volume mL/hour**	**Dosage / hour** **Bupivacaine (mg)**	**Dosage/ hour** **Fentanyl (microgram)**
Analgesia in labour	Lumbar epidural	8 - 15	10 – 18.75	16 - 30
Control of post operative pain	Thoracic, Upper / Lower abdominal epidural	6 - 15	7.5 - 18.75	12 - 30

Careful aspiration before starting the infusion is recommended to prevent intravascular injection. The infusion rate should be slow, with continual assessment of the patient in order to optimise efficacy and safety considerations for the patient and to avoid overdosage.

- Following the start of an infusion a continuous review of the patient is required, including periodic monitoring of the patient's blood pressure/pulse and assessment of pain and sedation at a minimum of 30 minute intervals.

Where conscious, verbal contact with the patient should be maintained throughout.

- Segmental testing of the level of the block is required at least at hourly intervals throughout the time the infusion is administered. Appropriate monitoring should be carried out to detect progressive spread of the block or an increasing density of block.
- Motor block should be assessed periodically using the Bromage score. For obstetric analgesia the test level T5/T6 should be clearly marked, for postoperative analgesia the level of block should be determined relative to the site of surgery.
- Routine maternal cardiovascular and foetal monitoring should be performed. In the case of labour, foetal heart rate should be monitored

every 5 minutes for 30 minutes and then as appropriate.

Hepatic / Renal Impairment
Since bupivacaine and fentanyl are metabolized in the liver and excreted via the kidneys, the possibility of medicine accumulation should be considered in patients with hepatic and/or renal impairment, with a possible reduction in dosage depending on the severity of their impairment.

Adequate filtering should be an integral part of the infusion line. The infusion line should be clearly marked to avoid confusion with intravenous lines. Also to avoid confusion, consideration should be given to using a different brand of proprietary pump to that used for IV infusions. In addition, the following pump specifications should be considered:

- accurate infusion rates down to 1 ml/hour should be able to be set.
- positive pressure drive, (not gravity feed), should be present.
- a back-up battery should be present.
- an automatic infusion shut-off should be present in case power is lost or the front of the pump is accidentally opened.

Elderly
Debilitated or elderly patients, including those with advanced liver disease or severe renal dysfunction should be given a reduced dosage commensurate with their physical condition.

Paediatric population
The use of bupivacaine with fentanyl in children is not recommended since experience in paediatric patients is limited.

Method of administration: Epidural use

Bufyl/ Bupivacaine and Fentanyl solution for infusion should only be administered epidurally and should only be used by or under the supervision of clinicians experienced in regional anaesthesia.

The dose administered must be tailored to the individual patient and procedure. When calculating the dosage for post-operative analgesia, the use of intra-operative bupivacaine and/or fentanyl (or other opioid agonist analgesic) should be taken into account. The rapid injection of bupivacaine with fentanyl solution should be avoided and the maximum accumulated dosage should not exceed 400 mg of bupivacaine and 720 micrograms of fentanyl for a 24 hour period in a 70 kg adult.

Note: This formulation is not to be used as a bolus.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1

The use of Bufyl/ Bupivacaine and Fentanyl solution for infusion is contraindicated in case of:

- acute respiratory depression,
- acute alcoholism,
- raised intracranial pressure or head injury. As for any narcotic analgesic, fentanyl should not be used in patients with or susceptible to respiratory depression, such as comatose patients who may have head injuries or a brain tumour. Fentanyl may obscure the clinical course of patients with head injury,
- hypovolaemia and complete heart block,
- intravenous regional anaesthesia (Bier's block) as unintentional passage of local anaesthetic into the systemic circulation, despite the use of a tourniquet, may cause systemic toxic reactions,
- obstetrical paracervical block anaesthesia,
- concurrent administration of monoamine oxidase inhibitors (MAOI's) or within 2 weeks of their discontinuation.

Epidural anaesthesia, regardless of the local anaesthetic used, has its own contraindications which include:

- active disease of the central nervous system such as meningitis, poliomyelitis, intracranial haemorrhage, subacute combined degeneration of the cord due to pernicious anaemia, spina bifida or meningomyelocele and cerebral or spinal tumours,
- tuberculosis of the spine,
- inflammation and/or pyogenic infection of the skin at or adjacent to the site of lumbar puncture,
- a diagnosed arteriovenous malformation in the vertebral column in close proximity to the proposed puncture site,
- cardiogenic shock,
- coagulation disorders or ongoing anticoagulant therapy,
- an expanding cerebral lesion, a tumour, cyst or abscess, which may, if the intracranial pressure is suddenly altered, cause obstruction to the cerebrospinal fluid or blood circulation (the pressure cone).

4.4 Special warnings and precautions for use

When any local anaesthetic agent is used, resuscitative equipment and medicines, including oxygen, should be immediately available to manage possible reactions involving the cardiovascular, respiratory or central nervous systems. Spinal and epidural anaesthesia may result in sympathetic block with resultant hypotension and bradycardia, therefore an intravenous cannula should be inserted before the local anaesthetic is injected.

In view of the risk of inadvertent intravascular injection which can produce toxic effects, bupivacaine should be given with great caution to patients with epilepsy, severe bradycardia, cardiac conduction disturbances, severe shock or severe digitalis intoxication.

Patients with uncorrected hypotension, coagulation disorders or patients receiving anti-coagulant treatment should receive epidural local anaesthetics with caution. Bupivacaine hydrochloride should be administered with caution to patients with cardiovascular disease, hypertension, hyperthyroidism or adrenocortical insufficiency.

Fentanyl should be used with caution in patients with cardiac bradyarrhythmias.

For continuous epidural analgesia the lowest possible effective concentration of local anaesthetic should be used. This will aid detection of neurological effects that might otherwise be masked by epidural blockade. Debilitated, elderly or young patients, including those with advanced liver disease orsevere renal impairment, may require reduced doses commensurate with their age and physical condition.

Since bupivacaine and fentanyl are metabolized in the liver and excreted via the kidneys, the possibility of medicine accumulation should be considered in patients with hepatic and/or renal impairment. As has been observed with all narcotic analgesics, episodes suggestive of Sphincter of Oddi Spasm may occur with fentanyl.

Local anaesthetics should be given with great caution (if at all) to patients with pre-existing abnormal neurological conditions, e.g. myasthenia gravis. Use with extreme caution in epidural and caudal anaesthesia when there are serious diseases of the CNS or of the spinal cord, e.g. meningitis, spinal fluid/ block, cranial or spinal haemorrhage, tumours, poliomyelitis, syphilis, tuberculosis,or metastatic lesions of the spinal cord.

Bupivacaine with fentanyl should be used with caution in patients with severe impairment of pulmonary function (chronic obstructive pulmonary disease e.g. bronchial asthma, patients with decreased respiratory reserve, or any patient with potentially compromised respiration) because of the possibility of respiratory depression. In such patients, narcotics may further decrease respiratory drive and increase airway resistance.

Certain forms of conduction anaesthesia, such as spinal anaesthesia and some peridural anaesthetics can alter respiration by blocking intercostal nerves. Fentanyl can also alter respiration through other mechanisms. Therefore, when bupivacaine with fentanyl is used to supplement these forms of anaesthesia, the physician should be familiar with the physiological alterations involved and be prepared to manage them in patients selected for this form of analgesia.

Patients allergic to ester derivatives of para-aminobenzoic acid (procaine, tetracaine, benzocaine etc.) have not shown cross sensitivity to agents of the amide type.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:

Concomitant use of Bufyl/ Bupivacaine and Fentanyl solution for infusion and

sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Bufyl/ Bupivacaine and Fentanyl solution for infusion concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

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

Tolerance and Opioid use disorder (abuse and dependence)
Tolerance, physical dependence, and psychological dependence may develop upon repeated administration of opioids.

Repeated use of opioids may lead to Opioid use disorder (OUD). Abuse or intentional misuse of opioids may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse.

A comprehensive patient history should be taken to document concomitant medications, including over the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance.

The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse, or addiction. The clinical need for analgesic treatment should be reviewed regularly.

Withdrawal syndrome
Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with fentanyl.

Repeated administration at short term intervals for prolonged periods may result in the development of withdrawal syndrome after cessation of therapy, which

may manifest by the occurrence of the following side effects: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, myalgia, mydriasis palpitations, irritability, agitation, hyperkinesia, nausea, vomiting, diarrhoea, anxiety, chills, tremor, weakness, insomnia, anorexia, abdominal cramps, increased blood pressure, increased respiratory rate or heart rate and sweating.

If women take this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

Hyperalgesia
Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and lessdefined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

This medicinal product contains 862 mg sodium per 250 ml of solution, equivalent to about 43% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Epidural anaesthesia is contra-indicated in patients receiving anticoagulant therapy. Cimetidine may prolong the effects of bupivacaine and fentanyl if used concurrently.

Bupivacaine
Local anaesthetics of the amide type, such as bupivacaine should be used with caution in patients receiving anti-arrhythmic medicines (e.g. amiodarone) since potentiation of cardiac effects may occur.

Other CNS depressant agents, e.g. barbiturates, neuroleptics, opioid agonists and general anaesthetics, will have additive or potentiating effects when used with bupivacaine with fentanyl. When patients have received such agents, the dose of bupivacaine with fentanyl required will be less than usual. Likewise, following the administration of bupivacaine with fentanyl, the dose of other CNS depressant agents should be reduced.

Bupivacaine should be used with care in patients receiving anti-arrhythmic drugs with local anaesthetic activity e.g. lignocaine or tocainide, since their toxic effects may be additive.
Antihypertensives like captopril and verapamil may cause severe hypotension and bradycardia in patients given epidural anaesthesia with bupivacaine. Beta-blockers, particularly propranolol, reduce the clearance of bupivacaine and may increase its toxicity.

Fentanyl

When a neuroleptic such as droperidol is used with fentanyl, pulmonary arterial pressure may be decreased. Hypotension can occur and, possibly hypovolaemia (which should be managed with appropriate parenteral fluids). The following adverse reactions have also been reported: chills, shivering, restlessness, hypertension, postoperative hallucinatory episodes, and transient periods of mental depression.

Extrapyramidal symptoms (dystonia, akathisia and oculogyric crisis) have been observed up to 24 hours postoperatively. When they occur, extrapyramidal symptoms can usually be controlled with antiparkinson agents.

Severe and unpredictable potentiation by MAO inhibitors has been reported with opioid agonist analgesics. Since the safety of bupivacaine with fentanylin this regard has not been established, the use of bupivacaine with fentanyl in patients who have received MAO inhibitors within 14 days is not recommended.

Nitrous oxide has been reported to produce cardiovascular depression when given with high doses of fentanyl. Profound bradycardia, sinus arrest and hypotension have occurred when patients receiving amiodarone have been given fentanyl for anaesthesia.

The respiratory depressant effect of fentanyl may be enhanced or prolonged by opioid premedication, barbiturates, benzodiazepines or related drugs, neuroleptics, halogenic gases, general anaesthetics, gabapentinoids (gabapentin and pregabalin) and other non-selective CNS depressants (e.g. alcohol).

When fentanyl is used in a single dose, the concomitant use of potent CYP3A4 inhibitors such as ritonavir requires special patient care and observation. With continuous treatment dose reduction of fentanyl may be required to avoid accumulation of fentanyl, which may increase the risk of prolonged or delayed respiratory depression.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Bupivacaine crosses the placenta to a lesser degree than lidocaine or mepivacaine following maternal injection. A lower foetal maternal ratio (0.2-0.4) than for other local anaesthetics (e.g. lignocaine, prilocaine) has been observed for bupivacaine. The greater degree of protein-binding of bupivacaine compared with these other drugs not only limits the amount of bupivacaine available to cross the placenta but also reduces the relative amount of free drug in the foetal circulation.

Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate.
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.
Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

Breast-feeding
With recommended doses, bupivacaine enters breast milk but in such small quantities at therapeutic dose levels that there is generally no risk of affecting the child.
Fentanyl has been shown to have an umbilical cord to maternal vein ratio of 0.06 to 0.44.
Administration to nursing women is not recommended as fentanyl may be secreted in breast milk and may cause respiratory depression in the infant.

4.7 Effects on ability to drive and use machines

This medicine has moderate influence on the ability to drive and use machines. Patients should be warned not to drive or operate machinery until all the effects of the anaesthesia and the immediate effects of surgery are passed. A formal clinical test of motor power is advised.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
    - The medicine has been prescribed to treat a medical or dental problem and
    - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and

It was not affecting your ability to drive safely

4.8 Undesirable effects

Bupivacaine
Reactions to bupivacaine are similar in character to those observed with other local anaesthetics of the amide type. Adverse reactions may be due to high

plasma levels as a result of excessive dosage, rapid absorption, delayed elimination or metabolism, or inadvertent intravascular injection.

Such reactions are systemic in nature and involve the central nervous system and/or the cardiovascular system. Inadvertent subarachnoid injection may lead to cardiovascular collapse, unconsciousness and respiratory arrest. An accidental intrathecal injection may be recognized by early signs of spinal block such as hypotension, bradycardia and difficulty in breathing.

The adverse reactions considered at least possibly related to treatment with bupivacaine hydrochloride from clinical trials with related products and post-marketing experience are listed below by body system organ class and absolute frequency. Frequencies are defined as 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) including isolated reports, or Not known (identified through post-marketing safety surveillance and the frequency cannot be estimated from the available data).

Table 2 - Adverse Drug Reactions (ADR) of bupivacaine

System Organ Class	Frequency Classification	Adverse Drug Reaction
Immune system disorders	Rare	Allergic reactions, bronchospasm, anaphylactic reaction/ shock (see section 4.4)
Nervous system disorders	Common	Nervousness, paraesthesia, dizziness
	Uncommon	Signs and symptoms of CNS toxicity (euphoria, disorientation, convulsions, circumoral paraesthesia, numbness of the tongue, hyperacusis, visualdisturbances, los of consciousness, tremor, light headedness, tinnitus, pruritus, diaphoresis, dysarthria, muscle twitching)
	Rare	Weakness, persistent anaesthesia, loss of sphincter control, neuropathy,peripheral nerve injury, arachnoiditis, paresis and paraplegia
Eye disorders	Rare	Diplopia, miosis
Cardiac disorders	Common	Bradycardia (see section 4.4)
	Rare	Cardiovascular collapse or cardiac arrest (see section 4.4), cardiac arrhythmias
Vascular disorders	Very Common	Hypotension (see section 4.4)
	Common	Hypertension (see section 4.5)
Respiratory, thoracic and mediastinal disorders	Rare	Laryngospasm, respiratory depression or respiratory arrest
Gastrointestinal disorders	Very Common	Nausea
	Common	Vomiting
Renal and urinary disorders	Common	Urinary retention

Fentanyl

The following table displays ADRs that have been reported with the use of fentanyl IV from either clinical trials or post-marketing experiences.

Table 3 - Adverse Drug Reactions (ADR) of fentanyl

System Organ Class	Adverse Drug Reactions
	Frequency Category

	Very Commo	Common	Uncommon	Not Known
Immune system disorders				Hypersensitivity (such as anaphylactic shock, anaphylactic reaction, urticaria)
Psychiatric disorders		Agitation	Changes in mood, hallucinations	Delirium Drug dependence (see section 4.4)
Nervous system disorders	Muscle rigidity (which may also involve the thoracic muscles)	Dyskinesia; sedation; dizziness, drowsiness, confusion	Headache, facial flushing, vertigo, restlessness	Convulsions; loss o consciousness; myoclonus; dyskinesia, raised intracranial pressure
Eye disorders		Visual disturbance	Miosis	
Cardiac disorders		Bradycardia; Tachycardia; Arrhythmia	Palpitations	Cardiac arrest
Vascular disorde		Hypotension; Hypertension; Venous pain	Phlebitis; blood pressure fluctuatio orthostatic hypotension	
Respiratory, thoracic and mediastinal disorders		Laryngospasm Bronchospasm Apnoea	Hyperventilation; Hiccups	Respiratory depression; Cough
Gastrointestinal disorders	Nausea; Vomiting		Dry mouth, constipation, dysphagia	
Skin and subcutaneous tissue disorders		Allergic dermatitis		Pruritus
General disorders and administration site conditions			Chills, hypothermia, sweating, micturition difficulties,	Drug withdrawal syndrome **(see section 4.4.)**
Injury, poisoning and procedural complications		Postoperative confusion	Airway complication of anaesthesia	

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 Yellow Card Scheme at: https://yellowcard.mhra.gov.uk/or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

With accidental intravascular injections, the acute toxic systemic effect of bupivacaine will be obvious within 1-3 minutes, while with overdosage, peak plasma concentrations may not be reached for 20-30 minutes depending on the site of injection with signs of toxicity thus being delayed. Toxic reactions originate mainly in the central nervous and the cardiovascular systems. Pronounced acidosis, hyperkalaemia or hypoxia in the patient may increase the risk and severity of toxic reactions.

Central nervous system toxicity is a graded response with symptoms and signs of escalating severity. The first symptoms are circumoral paraesthesia, numbness of the tongue, light-headedness, hyperacusis and tinnitus. Visual disturbance and muscular tremors are more serious and precede the onset of generalized convulsions. These signs must not be mistaken for a neurotic behaviour. Unconsciousness and grand malconvulsions may follow which may last from a few seconds to several minutes. Hypoxia and hypercarbia can occur rapidly following convulsions due to the increased muscular activity, together with the interference with normal respiration and loss of airway patency. In severe cases apnoea may occur.

Recovery due to redistribution of the local anaesthetic medicine from the central nervous system and metabolism may be rapid unless large amounts of the medicine have been injected.

During epidural analgesia, a marked fall in blood pressure and/or intercostal paralysis may be seen, possibly due to the use of excessive doses or due to improper positioning of the patient (e.g. women in labour).

Effects on the cardiovascular system may be seen in severe cases. Hypotension, bradycardia, arrhythmia and even cardiac arrest may occur as a result of high systemic concentrations. Cardiovascular toxic effects are generally preceded by signs of toxicity in the central nervous system, unless the patient is receiving a general anaesthetic or is heavily sedated with medicines such as a benzodiazepine or barbiturate.

Overdosage due to fentanyl may result in narcosis, cardiorespiratory depression accompanied by cyanosis, followed by a fall in body temperature, circulatory collapse, coma and possibly death.
Toxic leukoencephalopathy has been also observed with fentanyl overdose.

High doses of fentanyl may produce motor stimulation and muscle rigidity, particularly involving the muscles of respiration. Muscular rigidity may be associatedwith reduced pulmonary compliance and/or apnoea, laryngospasm or bronchospasm. This effect is related to the dose and speed of injection and may be reduced by slow infusion. It is unlikely to arise when recommended doses are used in epidural infusion.

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

Management

If signs of acute systemic toxicity appear, infusion of the local anaesthetic should be stopped immediately. If convulsions occur, they should be treated immediately. The objectives of treatment are to maintain oxygenation, stop the convulsions and support the circulation. Oxygen must be given, and ventilation assisted if necessary (mask and bag). An anticonvulsant should be given IV if the convulsions do not stop spontaneously in 15-20 seconds. Thiopentone 75-125 mg by slow intravenous injection will abort the convulsions rapidly.

Alternatively, intravenous diazepam 5-10 mg may be used, although its action is slower. If respiratory depression occurs, assisted respiration and, if necessary, intravenous administration of a single dose of a neuromuscular blocking agent compatible with the patient's condition, such as suxamethonium will provide adequateventilation without reversing analgesia. Suxamethonium which will stop the muscle convulsions rapidly, will require tracheal intubation and controlled ventilation and should only be used by those familiar with these procedures.

A specific narcotic antagonist, such as nalorphine or naloxone, should be available for use as indicated to manage respiratory depression. This does not preclude the use of more immediate countermeasures. Though opioid antagonists (e.g. naloxone) can immediately reverse the respiratory depression they will also reverse the central analgesic effect due to fentanyl, although the epidural analgesia may not be altered.The duration of respiratory depression following overdosage of fentanyl is usually longer than the duration of narcotic antagonist action.

Should circulatory arrest occur, immediate cardiopulmonary resuscitation should be instituted. In the presence of hypoventilation or apnoea, oxygen should be administered, and respiration assisted or controlled as necessary. A patent airway must be maintained. Optimal oxygenation and ventilation and circulatory support, as well as treatment of acidosis, are of vital importance since hypoxia and acidosis will increase the systemic toxicity of local anaesthetics. If cardiovascular depression is evident (hypotension, bradycardia), a pressor drug like ephedrine 3-6 mg should be given by slow intravenous injection and repeated, if necessary, every 3-4 minutes according to response to a maximum of 30 mg. Posture improvement with elevation of the legs, left lateral displacement (if pregnant) and prophylactic volume loading with intravenous fluids should be initiated as appropriate.

The patient should be carefully observed for 24 hours; body warmth and adequate fluid intake should be maintained. If severe or persistent hypotension occurs, the possibility of hypovolaemia should be considered and managed with appropriate parenteral fluid therapy.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Local anaesthetic, ATC code: N01B B51

Bupivacaine

Mechanism of Action:

Bupivacaine Hydrochloride is a long acting local anaesthetic of the amide type. It prevents the generation and conduction of the nerve impulse by decreasing the permeability of the nerve cell membrane to sodium ions. As well as blocking conduction in nerve axons in the peripheral nervous system, local anaesthetics interfere with the function of all organs in which conduction or transmission of impulses occur.

Clinical efficacy and safety

Systemic absorption of local anaesthetics produces effects on the cardiovascular and central nervous systems (CNS). At blood concentrations achieved with normal therapeutic doses, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are minimal. However, toxic blood concentrations depress cardiac conduction and excitability, which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest, sometimes resulting in fatalities. In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure. Recent clinical reports and animal research suggest that these cardiovascular changes are more likely to occur after unintended direct intravascular injection of bupivacaine. Therefore, when epidural anaesthesia with bupivacaine is considered, incremental dosing is necessary.

Fentanyl

Mechanism of action:

Fentanyl citrate a potent narcotic analgesic is a synthetic opiate with a clinical potency of 50 to 100 times that of morphine. Its onset of action is rapid and its duration of action is short.

Clinical efficacy and safety

In man, a single IV dose of 0.5-1 mg/70 kg body weight immediately produces a pronounced state of surgical analgesia, respiratory depression, bradycardia and other typical morphine-like effects. The duration of action of the peak effects is about 30 minutes. The principal actions of therapeutic value are analgesia and sedation. When used with a neuroleptic agent it can induce a state of neuroleptanalgesia. As with other narcotic analgesics, the effect of fentanyl on respiratory depression increases as the drug dosage is increased. All potent morphine-like drugs produce relief from pain, ventilatory

depression, emesis, constipation, physical dependence, certain vagal effects and varying degrees of sedation. Fentanyl, however, differs from morphine not only by its short duration of action but also by its lack of emetic effect and minimal hypotensive activity in animals. Epidural fentanyl enhances the epidural analgesia achieved with bupivacaine.

5.2 Pharmacokinetic properties

Bupivacaine

Bupivacaine is a long acting, amide type local anaesthetic chemically related to lignocaine and mepivacaine. It is approximately four times as potent as lignocaine. Bupivacaine has a pKa of 8.1 and is extensively bound to plasma proteins. Bupivacaine exhibits a high degree of lipid solubility with an oil/water partition coefficient of 27.5. These factors contribute to its prolonged duration of action.

The onset of blockade is slower than with lignocaine, especially when anaesthetizing large nerves. When used in low concentrations (2.5 mg/mL or less) there is less effect on motor nerve fibres and the duration of action is shorter. Low concentrations may, however, be used with advantage for prolonged pain relief, e.g. in labour or postoperatively.

Absorption:

Absorption of bupivacaine from the epidural space occurs in 2 phases; the first phase is in the order of 7 minutes and the second is in 6 hours. The slow absorption is rate-limiting in the elimination of bupivacaine, which explains why the apparent elimination half-life after epidural administration is longer than after intravenous administration.

Distribution:

After epidural injection peak plasma levels of bupivacaine in the blood are reached within 30 to 45 minutes, followed by a decline to insignificant levels during the next 3 to 6 hours. Intercostal blocks give the highest peak plasma concentration due to a rapid absorption (maximum plasma concentrations in the order of 1-4 mg/L after a 400 mg dose), while epidural and major plexus blocks result in intermediate plasma concentrations.. In children rapid absorption and high plasma concentrations (in the order of 1-1.5 mg/L after a dose of 3 mg/kg) are seen with caudal block.

Biotransformation and elimination:

Bupivacaine is excreted in the urine principally as metabolites with about 6% as unchanged medicine. Following epidural administration the urinary recovery of unchanged bupivacaine is about 0.2%, of pipecolylxylidine (PPX) about 1% and of 4-hydroxy-bupivacaine about 0.1% of the administered dose. Various pharmacokinetic parameters can be significantly altered by a number of factors including the presence of hepatic and renal disease, route of administration, age of the patient and certain concomitant medication. The drug crosses the placenta.

Fentanyl:

Absorption:

Fentanyl is a lipid-soluble drug and its pharmacokinetics can be described in terms of a three-compartment model. Following intravenous injection, there is

a short distribution phase during which high concentrations of fentanyl are achieved quickly in well-perfused tissues such as the lungs, kidneys and brain.
Distribution:
The drug is redistributed to other tissues; it accumulates more slowly in skeletal muscle and yet more slowly in fat, from which it is gradually released into the blood. Up to 80% of fentanyl is bound to plasma proteins.
Biotransformation and elimination:
Fentanyl is primarily metabolized in the liver, probably by N-dealkylation, and it is excreted mainly in the urine with less than 10% representing the unchanged drug. The drug clearance in ml/min/kg is 13±2 with a volume of distribution in litres/kg of 4.0±0.4. Estimates of terminal half-life of fentanyl range from 141 to 853 minutes with an average of 3.7 hours.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, Sodium hydroxide (for pH adjustment), Water for injections.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.. The pH range is 5.0 to 6.5.

6.3 Shelf life

3 years
After opening, the product should be used immediately. The product is for single use only and should not be used for more than 24 hours.

6.4 Special precautions for storage

Not applicable.

6.5 Nature and contents of container

250ml or 500ml polypropylene infusion bags in packs of 5.
Not all pack sizes may be marketed

6.6 Special precautions for disposal

Solutions showing discolouration and unused portions of solutions should be discarded. For single use only. Do not reconnect partially used bags.
No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7 MARKETING AUTHORISATION HOLDER

Sandoz Limited
Park View, Riverside Way
Watchmoor Park
Camberley, Surrey
GU15 3YL
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/1734

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07/02/2025

10 DATE OF REVISION OF THE TEXT

07/02/2025