

NEW ZEALAND DATA SHEET

Bupafen epidural infusion Solution for infusion

1 PRODUCT NAME

Bupafen epidural infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Bupafen consists of 1.25 mg/mL bupivacaine HCl and 2 µg/mL fentanyl citrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Infusion solution: a clear, colourless, particle-free solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Bupafen for epidural infusion is intended for post-operative or obstetric analgesia, except where specifically contraindicated.

4.2 Dose and method of administration

The lowest dosage that results in effective analgesia should be used and should be based on the status of the patient and the analgesia required.

Adults

Recommended dosages for infusion for analgesia in the average, healthy 70 kg adult patient.

Bupafen

Postoperative Analgesia: epidural

	VOLUME	BUPIVACAINE	FENTANYL
Epidural infusion (for up to 48 hours)	6 – 15 mL/hr	7.5 – 18.75 mg/hr	12 – 30 µg/hr

Note: Recommended doses

Toxic doses vary widely between patients. Careful observation of the patient must therefore be maintained. It is recommended that a single dose of bupivacaine at any time should not exceed 2 mg/kg. However the dose administered must be tailored to the individual patient and procedure, and the maximum dose quoted here should be used as a guide only.

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. When given by bolus injection, doses should not be repeated more frequently than every 3 hours. The maximum daily dosage should not exceed 400 mg bupivacaine in a 70 kg adult, whether administered by bolus injection and/or by infusion.

The rapid injection of a large volume of Bupafen solution should be avoided and fractional doses should be used when feasible.

Test dose

For epidural analgesia, a 3 –5 mL test dose of a local anaesthetic, preferably containing up to 15 µg of adrenaline (e.g. 3 mL Marcain 0.5% with Adrenaline 1:200,000) should be administered. Verbal contact and repeated monitoring of the heart rate and blood pressure should be maintained for 5 minutes after the test dose after which, in the absence of signs of subarachnoid or intravascular injection, the main dose may be given.

Use of a test dose containing adrenaline may have further advantages in that an intravascular injection of adrenaline will be quickly recognized by an increase in heart rate,

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usually within about 40 seconds. To detect this, the heart rate and rhythm should be monitored with an electrocardiogram. An accidental intrathecal injection may be recognized by signs of spinal block.

Prior to connection to an infusion set, aspiration should be repeated. The infusion rate should be slow, with continual assessment of the patient. If toxic symptoms or signs occur, the infusion should be stopped immediately.

Paediatrics

Experience with Bupafen in children is limited and its use is not recommended.

Debilited or Elderly Patients

Debilited or elderly patients, including those with partial or complete heart block, advanced liver disease or severe renal dysfunction should be given a reduced dosage commensurate with their physical condition. [see Section 4.4]

4.3 Contraindications

1. Allergy or hypersensitivity to amide type local anaesthetics. Detection of suspected sensitivity by skin testing is of limited value.
2. 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.
3. Obstetrical paracervical block anaesthesia.
4. Local anaesthetic techniques must not be used where there is inflammation and/or sepsis in the region of the proposed injection.
5. Epidural and spinal injections are contraindicated in patients with coagulation disorders or receiving anti-coagulation treatment.
6. Known intolerance to fentanyl.
7. Bronchial asthma. [see Section 4.4].
8. Head injuries and increased intracranial pressure: As for any narcotic analgesic, fentanyl should not be used in patients susceptible to respiratory depression, such as comatose patients who may have head injuries or a brain tumour. [see Section 4.4] Fentanyl may obscure the clinical course of patients with head injury.
9. Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics and the use of fentanyl in patients who have received MAO inhibitors within 14 days is not recommended [see Section 4.5].
10. Fentanyl may cause muscle rigidity upon IV administration. Therefore, the need for reversal and muscle relaxants contraindicates its use in patients with a history of myasthenia gravis.

4.4 Special warnings and precautions for use

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Bupafen with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anaesthetics, medicines with antihistamine-sedating actions such as antipsychotics, other

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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 medicine-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics [see Section 4.5].

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

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

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. Resuscitative equipment, oxygen and a narcotic antagonist should be readily available to manage apnoea. Because of the possibility of hypotension and bradycardia following major blocks, an IV cannula should be inserted before the local anaesthetic is injected. Delay in proper management of dose-related toxicity, under-ventilation from any cause and/or altered sensitivity may lead to the development of acidosis, cardiac arrest and death.

Injections should always be made slowly with frequent aspirations to avoid inadvertent intravascular injection, which can produce toxic effects.

Patients with uncorrected hypotension, coagulation disorders or patients receiving anti-coagulant treatment should receive epidural local anaesthetics with caution.

The safety and effectiveness of Bupafen depends on proper dosage, correct technique and adequate precautions. Standard textbooks should be consulted regarding specific techniques and precautions for various regional anaesthetic procedures.

The lowest dosage that results in effective anaesthesia should be used [see section 4.2]. Repeated injection of Bupafen may cause accumulation of bupivacaine or its metabolites and result in toxic effects. Tolerance to elevated blood levels varies with the status of the patient. Debilitated, elderly or young patients, including those with partial or complete conduction of block, advanced liver disease or severe renal impairment, should be given reduced doses commensurate with their age and physical condition.

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

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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.

Since bupivacaine and fentanyl are metabolised in the liver and excreted via the kidneys, the possibility of medicine accumulation should be considered in patients with hepatic and/or renal impairment [see section 4.2].

Bupivacaine should be used with caution in patients with genetic predisposition to malignant hyperthermia as the safety of amide local anaesthetic agents in these patients has not been fully established. A standard protocol for the management of malignant hyperthermia should be available.

Bupivacaine should be used with caution in patients with known agent sensitivities. Patients allergic to ester derivatives of para-aminobenzoic acid (procaine, tetracaine, benzocaine etc.) have not shown cross sensitivity to agents of the amide type.

If fentanyl is administered with neuroleptics, the user should be familiar with the special properties of each drug, particularly with regard to durations of action. In addition, when such a combination is used, fluids and other countermeasures to manage hypotension should be available.

Fentanyl is not recommended for use in patients who require the concomitant administration of Monoamine Oxidase Inhibitors (MAOIs) due to the risk of serotonin toxicity [see Section 4.5].

Depression of respiration is the most marked and dangerous side effect of fentanyl. In the post-operative period, patients may exhibit delayed depression of respiration. Patients should be monitored for this possibility and appropriate counter-measures taken as necessary. Respiratory depression caused by narcotic analgesics can be reversed by narcotic antagonists. Consult individual product information (nalorphine or naloxone) before employing narcotic antagonists.

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

Fentanyl may cause muscle rigidity, particularly involving the muscles of respiration. This effect is related to the dose and speed of injection and may be reduced by slow infusion. It is unlikely to arise following epidural injection. However, if this effect occurs, it may be managed by the use of assisted or controlled respiration and, if necessary, by administration of a neuromuscular blocking agent compatible with the patient's condition.

Opioid agonist analgesics have abuse potential. Bupafen is intended for short-term administration for the relief of obstetric and post-operative pain.

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 Bupafen is used to supplement

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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.

Fentanyl may produce bradycardia, which may be treated with atropine: however it should be used with caution in patients with cardiac bradyarrhythmias.

As has been observed with all narcotic analgesics, episodes suggestive of Sphincter of Oddi Spasm may occur with fentanyl.

4.5 Interaction with other medicines and other forms of interaction

Benzodiazepines and other Central Nervous System (CNS) Depressants	
Clinical Impact	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.
Intervention	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation [see Section 4.4].
Examples	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anaesthetics, drugs with antihistamine-sedating actions such as antipsychotics, other opioids, alcohol.

Anti-arrhythmic medicines

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

Other CNS depressants

Other CNS depressant agents, e.g. barbiturates, neuroleptics, opioid agonists and general anaesthetics, will have additive or potentiating effects when used with Bupafen. When patients have received such agents, the dose of Bupafen required will be less than usual. Likewise, following the administration of Bupafen, the dose of other CNS depressant agents should be reduced [see Section 4.4].

Neuroleptics

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.

Serotonergic Medicines including Monoamine Oxidase Inhibitors (MAOIs)

There have been reports of serotonin syndrome in a temporal connection with the therapeutic use of fentanyl in combination with serotonergic medicines such as selective serotonin reuptake inhibitors (SSRIs) and MAOIs. Signs of serotonin syndrome include confusion, agitation, fever, sweating, ataxia, hyperreflexia, diarrhoea and clonus (spontaneous, induced and myoclonus). Immediate withdrawal of the serotonergic medicines usually brings about a rapid improvement. Treatment depends on the nature and severity of the symptoms.

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Severe and unpredictable potentiation of opiate effects and/ or serotonergic effects by MAOIs has been reported with fentanyl. Fentanyl should not be used within 14 days after discontinuation of treatment with MAOIs.

Nitrous oxide

Nitrous oxide has been reported to produce cardiovascular depression when given with high doses of fentanyl.

Amiodarone

Profound bradycardia, sinus arrest and hypotension have occurred when patients receiving amiodarone have been given fentanyl for anaesthesia.

4.6 Fertility, pregnancy and lactation

Use in pregnancy

Narcotic analgesics may cause respiratory depression in the newborn infant. These products should only be used during labour after weighing the needs of the mother against the risk to the foetus. Bupafen will cross the placenta rapidly. A lower foetal maternal ratio (0.2-0.4) than for other local anaesthetics (e.g. lignocaine, prilocaine) has been observed for bupivacaine. Fentanyl has been shown to have an umbilical cord to maternal vein ratio of 0.06 to 0.44. Opioid agonist analgesics may cause respiratory depression in the newborn infant. During the last 2-3 hours before expected delivery, these products should therefore only be used after weighing the needs of the mother against the risk to the foetus.

There is no information on the safe use of bupivacaine and/or fentanyl during pregnancy and these products should only be used during pregnancy if the potential benefit justifies the potential risk to the foetus. This does not preclude their use for obstetric analgesia

Use in lactation

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.

At maternal serum levels of up to 0.45 µg/mL produced by the epidural use of bupivacaine for vaginal delivery, bupivacaine could not be detected in breast milk during the first 24 hours after delivery (detection limit 0.02 µg/mL).

Following fentanyl 100 µg administered as a single bolus epidural dose there was no detectable excretion of medicine into breast milk.

4.7 Effects on ability to drive and use machines

Depending on dosage, local anaesthetics may have a very mild effect on mental function and may temporarily impair locomotion and co-ordination.

4.8 Undesirable effects

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.

Pronounced acidosis, hyperkalaemia or hypoxia in the patient may increase the risk and severity of toxic reactions.

Such reactions are systemic in nature and involve the central nervous system and/or the cardiovascular system [see Section 4.9]. Inadvertent subarachnoid injection may lead to

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cardiovascular collapse, CNS depression and respiratory arrest. Reactions to fentanyl are similar to those observed with other opioid agonist analgesics.

More Common Reactions

Light-headedness, nervousness, dizziness, blurred vision, tremor, tinnitus, oral numbness, disorientation, nausea and vomiting, respiratory depression (related to fentanyl), apnoea, muscular rigidity, bradycardia and pruritis. If these respiratory and cardio-vascular effects remain untreated, respiratory arrest, circulatory depression, or cardiac arrest could occur.

If respiratory depression occurs, assisted or controlled respiration will provide adequate ventilation without reversing analgesia. Respiratory depression can be immediately reversed by opioid antagonists (e.g. naloxone) which, it should be noted, will also reverse the central analgesia due to fentanyl, although the epidural analgesia may not be altered.

Muscular rigidity may be associated with reduced pulmonary compliance and/or apnoea, laryngospasm or bronchospasm. Prompt reversal of this effect can be achieved with the intravenous administration of an appropriate single dose of a muscle relaxant such as suxamethonium. Assisted or controlled respiration is required to provide ventilation after the use of muscle relaxants.

Bradycardia and other cholinergic effects may occur and can be controlled with the appropriate dose of atropine. The inclusion of atropine or other anticholinergic agents in the pre-anaesthetic regimen tends to reduce the occurrence of such effects.

Less Common Reactions

More serious but less common reactions that reflect an overdosage of bupivacaine are convulsions, unconsciousness, respiratory depression or arrest, hypotension, cardiovascular collapse and bradycardia which may lead to cardiac arrest.

Other less common reactions which may occur include: hypertension, hypotension, emesis, miosis, laryngospasm, diaphoresis, itching and euphoria.

High doses of fentanyl may produce motor stimulation and bronchospasm.

The incidence of adverse neurological reactions associated with the use of local anaesthetics is very low. Neurological reactions after regional anaesthesia have included persistent anaesthesia, paraesthesia, weakness, paralysis of the lower extremities and loss of sphincter control. Reactions to bupivacaine are similar in character to those observed with other local anaesthetics of the amide type

Allergy

Allergy to amide type local anaesthetics is very rare but may present as allergic dermatitis, bronchospasm or anaphylaxis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

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4.9 Overdose

Symptoms

Acute systemic toxicity: With accidental intravascular injections, the toxic effect 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.

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 mal convulsions may follow which may last from a few seconds to several minutes. Hypoxia and hypercarbia occur rapidly following convulsions due to the increased muscular activity, together with the interference with normal respiration and loss of the airway. In severe cases apnoea may occur. Acidosis increases the toxic effects of local anaesthetics.

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

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 (which may be preceded by marked skeletal muscle rigidity), cardiorespiratory depression accompanied by cyanosis, followed by a fall in body temperature, circulatory collapse, coma and possibly death.

Treatment of Overdosage

If signs of acute systemic toxicity appear, injection of the local anaesthetic should be immediately stopped.

Treatment will be required if convulsions occur. All medicines and equipment should be immediately available. 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 sec. Thiopentone 100-150 mg IV will abort the convulsions rapidly.

Alternatively diazepam 5-10 mg IV may be used, although its action is slower. Suxamethonium will stop the muscle convulsions rapidly, but will require tracheal intubation and controlled ventilation and should only be used by those familiar with these procedures. If cardiovascular depression is evident (hypotension, bradycardia), ephedrine 5-10 mg IV should be given and repeated, if necessary, after 2-3 min.

Should circulatory arrest occur, immediate cardiopulmonary resuscitation should be instituted. 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

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toxicity of local anaesthetics. Adrenaline (0.1-0.2 mg intravenous or intracardiac) should be given as soon as possible and repeated, if necessary.

In the presence of hypoventilation or apnoea, oxygen should be administered and respiration assisted or controlled as necessary. A patent airway must be maintained. 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 parental fluid therapy.

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. The duration of respiratory depression following overdose of fentanyl is usually longer than the duration of narcotic antagonist action.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

As with other narcotic analgesics, the duration of the respiratory depressant effect of fentanyl may be longer than the analgesic effect. The following observations have been reported concerning altered respiratory response to CO₂ stimulation following administration of fentanyl to man:

1. Diminished sensitivity to CO₂ stimulation may persist longer than depression of respiratory rate. Fentanyl frequently slows the respiratory rate.
2. Altered sensitivity to CO₂ stimulation has been demonstrated for up to four hours following a single intravenous dose of 600 µg fentanyl to healthy volunteers.
3. Duration and degree of respiratory depression is dose related.
4. The peak respiratory depressant effect of a single intravenous dose of fentanyl is noted 5 to 15 minutes following injection [see Section 4.4 concerning respiratory depression).

Bupivacaine

Bupivacaine, like other local anaesthetics, causes a reversible blockade of impulse propagation along nerve fibres by preventing the inward movement of sodium ions through the nerve membrane. Local anaesthetics of the amide type are thought to act within the sodium channels of the nerve membrane.

Local anaesthetic medicines may have similar effects on excitable membranes in the brain and myocardium. If excessive amounts of medicine reach the systemic circulation rapidly, symptoms and signs of toxicity will appear emanating mainly from the central nervous and cardiovascular systems.

Central nervous system toxicity usually precedes the cardiovascular effects as it occurs at lower plasma concentrations. Direct effects of local anaesthetics on the heart include slow conduction, negative inotropism and eventually cardiac arrest.

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Indirect cardiovascular effects (hypotension, bradycardia) may occur after epidural or spinal administration depending on the extent of the concomitant sympathetic block.

Fentanyl

Fentanyl is a narcotic analgesic. A dose of 100 µg of Fentanyl is approximately equivalent in analgesic activity to 10 mg of morphine or 75 – 100 mg of pethidine administered IV or IM. The principal actions of therapeutic value are analgesia and sedation. Alterations in respiratory rate and alveolar ventilation associated with narcotic analgesics may last longer than the analgesic effect. As the dose of narcotic is increased, the decrease in pulmonary exchange becomes greater. Large doses may produce apnoea. Fentanyl appears to have less emetic activity than either morphine or pethidine. Histamine assays and skin wheal testing in man indicate that clinically significant histamine release rarely occurs with fentanyl. Recent assays in man show no clinically significant histamine release at doses up to 50 µg/kg (0.05 mg/kg or 1 mL/kg). Fentanyl preserves cardiac stability and blunts stress-related hormonal changes at higher doses.

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.

In concentrations of 5 mg/mL it has a long duration action, from 2-5 hours following a single epidural injection and up to 12 hours after peripheral nerve blocks. The onset of blockade is slower than with lignocaine, especially when anaesthetising 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.

The plasma concentration of bupivacaine depends upon the dose, the route of administration and the vascularity of the injection site.

After injection of Bupafen solutions for caudal, epidural or peripheral nerve block in man, 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 subcutaneous abdominal injections give the lowest plasma concentration. Epidural and major plexus blocks are intermediate. 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.

Bupivacaine has a total plasma clearance of 0.58 L/min, a volume of distribution at steady state of 73 L, an elimination half-life of 2.7 h and an intermediate hepatic extraction ratio of 0.4 following experimental IV administration in adults. The terminal elimination half-life is prolonged in the newborn to approximately 8 hours. In children over 3 months the elimination half-life is similar to that in adults. Bupivacaine is mainly bound to alpha-1-acid glycoprotein in plasma with a plasma binding of 96%.

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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.

An increase in alpha-1-acid glycoprotein, which occurs postoperatively after major surgery, may cause an increase in the total plasma concentration of bupivacaine. The level of free medicine will remain the same. This explains why total plasma concentrations above the apparent toxic threshold level of 2.6-3.0 mg/L are well tolerated.

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 pipercolylxylidine (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.

Fentanyl

The pharmacokinetics of fentanyl can be described by a three-compartment model, with a distribution time of 1.7 minutes, redistribution of 13 minutes and a terminal elimination half-life of 219 minutes. The volume of distribution is 4 L/kg.

Fentanyl plasma protein binding capacity decreases with increasing ionisation of the agent. Alterations in pH may affect its distribution between plasma and the central nervous system. It accumulates in skeletal muscle and fat, and is released slowly into the blood. Fentanyl is primarily biotransformed in the liver. Approximately 75% of an intravenous dose is excreted in urine as metabolites with less than 10% representing the unchanged medicine. Approximately 9% of the dose is recovered in the faeces, primarily as metabolites.

5.3 Preclinical safety data

No information held by the sponsor.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride
Water for Injection

6.2 Incompatibilities

Local anaesthetics react with certain metals and cause the release of their respective ions which, if injected, may cause severe local irritation. Adequate precautions should be taken to avoid prolonged contact of Bupafen solutions and metal surfaces such as metal bowls, cannulae and syringes with metal parts. Solutions showing discolouration and unused portions of solutions should be discarded.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25°C. Do not refrigerate or freeze.

6.5 Nature and contents of container

Bupafen is available in 100 mL and 200 mL IV bags with overwraps

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6.6 Special precautions for disposal <and other handling>

No special requirements.

7 MEDICINE SCHEDULE

Controlled Drug B3

8 SPONSOR

Biomed Limited
52 Carrington Road
Point Chevalier
Auckland

Phone: 0800 833 133

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
25 October 2001

10 DATE OF REVISION OF THE TEXT

22 November 2019

SUMMARY TABLE OF CHANGES

DATE	CHANGE
22/11/19	Update to section 6.4 to include Do not refrigerate or freeze.
26/02/19	Update to SPC format; Update as per MARC recommendation dated 12/04/2017 (warnings and precautions, interactions with other medicines section). Storage condition corrected to store at or below 25°C in section 6.4, remove references to Propyflex bag and replace with IV bags with overwraps from sections 6.3 and 6.5.