PRODUCT INFORMATION

BUPIVACAINE 0.5% WITH ADRENALINE 1:200,000 PHEBRA

[bupivacaine hydrochloride and adrenaline (epinephrine)] solution for injection

NOT FOR INTRAVENOUS ADMINISTRATION UNDER ANY CIRCUMSTANCES

1 NAME OF THE MEDICINE

bupivacaine hydrochloride monohydrate
adrenaline (epinephrine) acid tartrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Bupivacaine 0.5% with Adrenaline 1:200,000 Phebra solution for injection contains bupivacaine hydrochloride 100 mg/20 mL with adrenaline (epinephrine) (as acid tartrate) 100 micrograms/20 mL.

The pH of the solution is between 3.0 - 5.5.

Excipient with known effect: contains sulfites.

For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

Bupivacaine 0.5% with Adrenaline 1:200,000 Phebra is a sterile, clear, colourless, or almost colourless isotonic aqueous solution for injection or infusion.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Bupivacaine 0.5% with Adrenaline 1:200,000 Phebra is indicated for the production of local or regional anaesthesia and analgesia in individuals as follows:

Surgical anaesthesia

- Epidural block for surgery
- Field block (minor and major nerve blocks and infiltration)

Analgesia

- Intermittent bolus epidural administration for analgesia in postoperative pain or labour pain
- Field block (minor nerve block and infiltration)

4.2 DOSE AND METHOD OF ADMINISTRATION

Bupivacaine 0.25% with adrenaline (epinephrine) solution for injection, and bupivacaine 0.125%, 0.25%, 0.375% and 0.5% solutions for injection, are unavailable in this brand however are available in other brands.

Where correct dosing requires a lower concentration of bupivacaine with adrenaline (epinephrine), or a bupivacaine solution without adrenaline (epinephrine), products from other suppliers should be used.

As with all local anaesthetics, the dosage varies and depends upon the area to be anaesthetised, the vascularity of the tissues, the number of neuronal segments to be blocked, the depth of anaesthesia and degree of muscle relaxation required, individual tolerance, the technique of anaesthesia, and the physical condition of the patient.

The lowest dosage that results in effective anaesthesia should be used. In general, surgical anaesthesia requires the use of higher concentrations and doses than those required for analgesia. The volume of the drug used will affect the extent of spread of anaesthesia.

Bupivacaine 0.5% with Adrenaline 1:200,000 Phebra is for single use only. Use in one patient on one occasion only and discard. Contains no antimicrobial preservative

The following tables are a guide to dosage. The clinician's experience and knowledge of the patient's physical status are of importance in deciding the dose. Studies to date indicate that 400 mg administered over 24 hours is well tolerated in average adults.

Bupivacaine 0.5% with Adrenaline 1:200,000 Phebra should not be used for epidural block in labour analgesia (apart from the use as a test dose) as the benefits from the addition of adrenaline (epinephrine) have not been shown to outweigh the risks.

Dosage recommendations for bupivacaine solutions for injection, with or without adrenaline (epinephrine), for various anaesthetic procedures in an average, healthy 70 kg adult patient. Generally, the dose of local anaesthetic solutions containing adrenaline equals that of plain solutions.

TABLE 1: RECOMMENDED DOSAGE FOR SURGICAL ANAESTHESIA

SURGICAL ANAESTHESIA	Conc mg/mL	Dose mL	Dose mg
Lumbar Epidural			
Abdominal, pelvic and lower limb surgery, including Caesarean section	5.0	15 - 30	75 - 150
Thoracic Epidural			
Upper abdominal and thoracic surgery	2.5#	5 - 15	12.5 - 37.5
	5.0	5 - 10	25 - 50
Caudal Epidural	2.5#	15 - 40	37.5 - 100
	5.0	15 - 25	75 - 125
Other blocks			
Local infiltration	2.5#	5 - 60	12.5 - 150
	5.0	5 - 30	25 - 150
Intercostal (per segment)	2.5#	4 - 8	10 - 20
	5.0	3 - 5	15 -25
Brachial plexus	5.0	20 - 30	100 - 150
Sciatic	5.0	10 - 20	50 - 100
3 in 1 (Femoral, obturator and lateral cutaneous)	5.0	10 - 20	50 - 100
Pudendal	2.5# - 5.0	5 - 10 each side	7.5 - 100

This concentration is not available in this brand. Where correct dosing requires this concentration of bupivacaine with adrenaline (epinephrine), or a bupivacaine solution without adrenaline (epinephrine), please refer to the appropriate product information document.

TABLE 2: RECOMMENDED DOSAGE FOR ANALGESIA, INCLUDING CONTINUOUS INFUSION

ANALGESIA	Conc mg/mL	Dose	
Caudal Epidural Postoperative pain management	2.5#	20 - 30 mL bolus	50 - 75 mg bolus
Lumbar Epidural Bolus (incl. labour pain management)	2.5#- 5.0	6 - 12 mL bolus followed by	15 - 60 mg bolus followed by
Continuous infusion (incl. labour pain and postoperative pain management)	1.25*#	10 - 15 mL/hour	12.5 - 18.75 mg/hour
	2.5#	5 - 7.5 mL/hour	12.5 - 18.75 mg/hour
Thoracic Epidural Continuous infusion for postoperative pain management	1.25*#	5 - 10 mL/hour	6.25 - 12.5 mg/hour

* This solution is mainly used for epidural administration in combination with a suitable opioid for postoperative pain management. For further details of procedures please see current, standard textbooks.

This concentration is not available in this brand. Where correct dosing requires this concentration of bupivacaine with adrenaline (epinephrine), or a bupivacaine solution without adrenaline (epinephrine), please refer to the appropriate product information document.

Note:

1. Recommended doses

Tolerability varies widely between patients and toxic effects may occur after any local anaesthetic procedure. Careful observation of the patient must therefore be maintained. It is recommended that the dose of bupivacaine and adrenaline (epinephrine) containing solutions 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.

2. Injection

Injection of repeated doses of bupivacaine may cause significant increase in blood levels with each repeated dose, due to accumulation of the drug or its metabolites, or due to slow metabolic degradation.

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

3. Hypotension

During thoracic, lumbar and caudal epidural anaesthesia/analgesia, a marked fall in blood pressure and/or intercostal paralysis may be seen, possibly due to the use of excessive doses, improper positioning of the patient or accidental disposition of the anaesthetic within the subarachnoid space. Hypotension and bradycardia may occur as a result of sympathetic blockade.

4. Test dose

For epidural anaesthesia, a test dose of 3 - 5 mL of a local anaesthetic solution, preferably containing up to 15 micrograms of adrenaline (epinephrine), (e.g. 3 mL Bupivacaine 0.5% with Adrenaline 1:200,000 Phebra) should be administered. Verbal contact and repeated monitoring of heart rate and blood pressure should be maintained for 5 minutes following 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 (epinephrine) may have further advantages in that an intravascular injection of adrenaline (epinephrine) will be quickly recognised by an increase in heart rate, 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 recognised by signs of a spinal block.

Prior to administration of the total dose, aspiration should be repeated. The main dose should be injected **slowly** at a rate of 25 - 50 mg/min, while closely observing the patient's vital functions and maintaining verbal contact. If toxic symptoms or signs occur, the injection should be stopped immediately.

5. Prolonged blocks

When prolonged blocks are used, either by continuous infusion or by repeated bolus administration, the risks of reaching a toxic plasma concentration or inducing a local neural injury must be considered.

Use in Children

Experience with bupivacaine in children under the age of 12 is limited. The dosage in children should be calculated on a weight basis up to 2 mg/kg. The addition of adrenaline (epinephrine) will prolong the duration of the block by 50 - 100%.

Use in Pregnancy

It should be noted that the dose should be reduced in patients in the late stages of pregnancy.

Use in Debilitated or Elderly Patients

Debilitated 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 Special Warnings and Precautions).

4.3 CONTRAINDICATIONS

1. Allergy or hypersensitivity to amide type local anaesthetics or sodium metabisulfite in adrenaline (epinephrine) containing solutions. Detection of suspected hypersensitivity by skin testing is of limited value.

2. Epidural and spinal anaesthesia is contraindicated in patients with uncorrected hypotension.

3. Local anaesthetic techniques must not be used when there is infection in the region of the proposed injection and/or in the presence of septicaemia.

4. Bupivacaine is contraindicated in obstetric paracervical block, intravenous regional anaesthesia (Bier's block) and all intravenous infusions.

5. General contraindications related to epidural anaesthesia, regardless of the local anaesthetic used, should be taken into account.

The following are additional contraindications for solutions with adrenaline (epinephrine):

6. Adrenaline (epinephrine) is contraindicated in conditions where the production or exacerbation of tachycardia may prove fatal, such as thyrotoxicosis or severe heart disease, or in obstetrics when maternal blood pressure exceeds 130/80 mm Hg.

7. Solutions with adrenaline (epinephrine) must not be used for local analgesia in parts of the body with compromised blood supply or which are supplied by end arteries, such as fingers, toes, nose, ears or penis. There is a possibility of producing arterial vasoconstriction and subsequent ischaemic gangrene distal to the site of injection.

8. Solutions with adrenaline (epinephrine) should not be used in patients with a known sensitivity to sympathomimetic amines.

9. Solutions with adrenaline (epinephrine) should not be used in most patients with cerebral arteriosclerosis.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

1. When any local anaesthetic agent is used, resuscitative equipment and drugs, including oxygen, should be immediately available in order to manage possible adverse reactions involving the cardiovascular, respiratory or central nervous systems.

   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.

2. INJECTION SHOULD ALWAYS BE MADE SLOWLY WITH FREQUENT ASPIRATIONS TO AVOID INADVERTENT INTRAVASCULAR INJECTION WHICH CAN PRODUCE TOXIC EFFECTS (See Section 4.2 Dose and Method of Administration – Test dose).

3. Although intra-articular continuous infusions of local anaesthetics following arthroscopic and other surgical procedures is an unapproved use, there have been post-marketing reports of chondrolysis in patients receiving such infusions. The majority of reported cases of chondrolysis have involved the shoulder joint; cases of gleno-humeral chondrolysis have been described in paediatric and adult patients following intra-articular continuous infusions of local anaesthetics with and without adrenaline (epinephrine) for periods of 48 to 72 hours. There is insufficient information to determine whether shorter infusion periods are not associated with these findings. The time of onset of symptoms, such as joint pain, stiffness and loss of motion can be variable, but may begin as early as the 2nd month after surgery. Currently, there is no effective treatment for chondrolysis; patients who experienced chondrolysis have required additional diagnostic and therapeutic procedures and some required arthroplasty or shoulder replacement. Therefore, Bupivacaine 0.5% with Adrenaline 1:200,000 Phebra should not be used for post-operative intra-articular continuous infusion.

4. Careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness should be accomplished after each local anaesthetic injection. It should be kept in mind that at such times restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression or drowsiness may be early warning signs of CNS toxicity.

5. The use of local anaesthetics for major peripheral nerve block may involve the administration of large volumes in highly vascularised areas, often close to large blood vessels. As such there is an increased risk of intravascular injection and/or systemic absorption which can lead to high plasma concentrations. There have been reports of cardiac arrest or death during the use of bupivacaine for epidural anaesthesia or peripheral nerve blockade. In some instances, resuscitation has been difficult or impossible despite apparently adequate preparation and management.

6. Central nerve blocks may cause cardiovascular depression, especially in the presence of hypovolaemia. Epidural anaesthesia should be used with caution in patients with impaired cardiovascular function. Epidural anaesthesia may lead to hypotension and bradycardia. Hypotension should be treated promptly.

7. LOW MOLECULAR WEIGHT HEPARINS AND HEPARINOIDS (Spinal/Epidural Haematomas) – When neuraxial anaesthesia (epidural / spinal anaesthesia) is employed, patients anti-coagulated or scheduled to be anti-coagulated with low molecular weight heparins or heparinoids are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk of these events is increased by the use of indwelling epidural catheters, traumatic or repeated epidural/spinal puncture, and the concomitant use of drugs affecting haemostasis such as NSAID, platelet inhibitors or other anticoagulants. Patients should be frequently monitored for signs and symptoms of neurological impairment.

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

9. The lowest dosage that results in effective anaesthesia should be used (see Section 4.2 Dosage and Method of Administration). Repeated injection of bupivacaine 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. Elderly, young or debilitated patients, including those with partial or complete conduction block, advanced liver disease or severe renal impairment, should be given reduced doses commensurate with their age and physical condition.

10. Bupivacaine may cause acute toxicity effects on the central nervous and cardiovascular systems if utilised for local anaesthetic procedures resulting in high blood concentrations of the drug. This is especially the case after unintentional intravascular administration. Ventricular arrhythmia, ventricular fibrillation, sudden cardiovascular collapse and death have been reported in connection with high systemic concentrations of bupivacaine.

11. Bupivacaine should be given with caution to patients with epilepsy, impaired cardiac conduction, bradycardia, severe shock or digitalis intoxication. It should also be administered with caution to patients with impaired cardiovascular function as they may be less able to compensate for functional changes

associated with the prolongation of AV conduction produced by bupivacaine. Patients being treated with anti-arrhythmic drugs class III (e.g. amiodarone) should be under close surveillance and ECG monitoring since cardiac effects may be additive.
In patients with Stokes-Adams syndrome or Wolff-Parkinson-White syndrome extreme care should be taken to avoid accidental arterio- venous injection.

12. Local anaesthetics should be given with great caution (if at all) to patients with pre-existing neurological or neuromuscular disease, e.g. myasthenia gravis. Use with extreme caution in epidural, caudal and spinal 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.

13. Inadvertent intravascular or subarachnoid injection of small doses of local anaesthetics injected into the head and neck area, including retrobulbar, dental and stellate ganglion blocks, may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. Injections made inadvertently into an artery may cause immediate cerebral symptoms even at low doses.

    Clinicians who perform retrobulbar blocks should be aware that there have been reports of cardiovascular collapse and apnoea following the use of local anaesthetic injections for retrobulbar block. Prior to retrobulbar block, necessary equipment, drugs and personnel should be immediately available as with all other regional procedures. Retrobulbar injections may very occasionally reach the subarachnoid space, causing temporary blindness, cardiovascular collapse, apnoea, convulsions etc. These must be diagnosed and treated promptly.

    Retro- and peribulbar injections of local anaesthetics carry a low risk of persistent ocular muscle dysfunction. The primary causes include trauma and/or local toxic effects on muscles or nerves. The severity of such tissue reactions is related to the degree of trauma, the concentration of the local anaesthetic and the duration of exposure of the tissue to the local anaesthetic. For this reason, as with all local anaesthetics, the lowest effective concentration and dose of local anaesthetic should be used. Vasoconstrictors may aggravate tissue reactions and should be used only when indicated.

14. Fetal bradycardia/tachycardia frequently follows paracervical block with some amide type local anaesthetics and may be associated with fetal acidosis and hypoxia. Added risk appears to be present in prematurity, toxaemia of pregnancy, and fetal distress. Careful monitoring of the fetal heart rate is necessary. (see Section 4.3 Contraindications).

15. Bupivacaine should be used with caution in patients with known drug sensitivities.

16. Solutions containing adrenaline (epinephrine) also contain sodium metabisulfite which may cause allergic type reactions including anaphylactic type symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than non-asthmatic people.

17. Solutions containing adrenaline (epinephrine) should be used with extreme caution in patients with severe or untreated hypertension, poorly controlled thyrotoxicosis, ischaemic heart disease, heart block, cerebrovascular insufficiency, advanced diabetes and any other pathological condition that might be

aggravated by the effects of adrenaline (epinephrine) (see Section 4.3 Contraindications). Adrenaline (epinephrine) may induce anginal pain in patients suffering from ischaemic heart disease.

18. Solutions containing adrenaline (epinephrine) should be used with caution in patients with ventricular fibrillation, prefibrillatory rhythm, tachycardia, myocardial infarction, phenothiazine induced circulatory collapse and prostatic hypertrophy (see Section 4.3 Contraindications, 4.5 Interactions with other Medicines and Other Forms of Interactions and 4.8 Adverse Effects (undesirable effects)).

19. Hepatic dysfunction, with reversible increases of alanineaminotransferase (ALT), alkaline phosphates (AlkP) and bilirubin, has been observed following repeated injections or long-term infusions of bupivacaine. Association between bupivacaine use and the development of drug-induced liver injury (DILI) has been reported in a small number of literature reports especially with prolonged use. While the pathophysiology of this reaction remains unclear, immediate withdrawal of bupivacaine has shown rapid clinical improvement. If signs of hepatic dysfunction are observed during administration with bupivacaine, the medicinal product should be discontinued.

Use in hepatic impairment

Bupivacaine is eliminated primarily by hepatic metabolism and changes in hepatic function may have significant consequences. Bupivacaine has an intermediate clearance which depends on its unbound fraction and intrinsic metabolic clearance. Bupivacaine should therefore be used with caution in patients with severe hepatic disease.

Use in renal impairment

Bupivacaine should be used with caution in patients with severe renal dysfunction because acidosis and reduced plasma protein concentration, which are frequently seen in these patients, may increase the risk of systemic toxicity. Patients with hyperthyroidism are also more susceptible to toxicity with bupivacaine.

Use in the elderly

Please see 4.2 Dose and Method of Administration - Use in Debilitated or Elderly Patients.

Paediatric use

Caution should be used when administering bupivacaine to children under 12 years of age.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

1. Anti-arrhythmic drugs

Local anaesthetics of the amide type, such as bupivacaine, should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics e.g. certain antiarrhythmic drugs such as mexiletine and lidocaine (lignocaine), since potentiation of cardiac effects may occur.
Specific interaction studies with bupivacaine and anti-arrhythmic drugs class III (e.g. amiodarone) have not been performed, but caution should be advised (see Section 4.4 Special Warnings and Precautions for Use).

In addition, the following interactions may occur with solutions containing adrenaline (epinephrine).

2. CNS acting drugs

Solutions containing adrenaline (epinephrine) should be used with extreme caution in patients receiving tricyclic antidepressants, or monoamine oxidase (MAO) inhibitors as severe, sustained hypertension may result. The effects of adrenaline (epinephrine) may be potentiated by some antihistamines and thyroid hormones (see Section 4.4 Special Warnings and Precautions for Use). Phenothiazines and butyrophenones may reduce or reverse the pressor effect of adrenaline (epinephrine).

3. Oxytocic drugs of the ergot type

Solutions with adrenaline (epinephrine) should not be used in the presence of oxytocic drugs of the ergot-type as they are known to interact to produce severe, persistent hypertension and its subsequent sequelae.

4. Adrenergic neuron blocking agents

Solutions with adrenaline (epinephrine) should be used with caution in the presence of adrenergic neuron blocking agents (e.g. guanethidine, debrisoquine, bethanidine).

5. Beta Blockers

Non-cardioselective beta blockers such as propranolol enhance the pressor effects of adrenaline (epinephrine) which may lead to severe hypertension and bradycardia.

6. Inhalation anaesthetics

Serious cardiac arrhythmias and acute pulmonary oedema if hypoxia is present may occur if preparations containing adrenaline (epinephrine) are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichlorethylene, or other halogenated compounds.

7. Cardiac glycosides

Solutions with adrenaline (epinephrine) may interact with cardiac glycosides resulting in cardiac arrhythmias.

8. Quinidine

Solutions with adrenaline (epinephrine) may interact with quinidine resulting in cardiac arrhythmias.

9. Hypoglycaemia

Adrenaline (epinephrine)-induced hyperglycaemia may lead to loss of blood sugar control in diabetic patients treated with hypoglycaemic agents.

10. Alkaline solutions

The solubility of bupivacaine is limited at pH values above 6.5. This must be taken into consideration if adding an alkaline solution since precipitation might occur at higher pH values.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Effects on fertility have not been determined.

Use in pregnancy – Pregnancy Category A

After epidural administration of bupivacaine to women in labour, bupivacaine crosses the placental barrier. However, concentrations in umbilical veins are lower than those found in the maternal circulation.

Bupivacaine has been effectively used for obstetrical analgesia and adverse effects on the course of labour or delivery are rare. It has been suggested that blood glucose levels should be checked in newborns after obstetric regional anaesthesia.

Fetal adverse effects due to bupivacaine, such as fetal bradycardia, seem to be most apparent in paracervical block anaesthesia. Such effects may be due to high concentrations of anaesthetic reaching the fetus (refer Section 4.3 Contraindications).

The safe use of bupivacaine during pregnancy, other than labour, has not been established. Although bupivacaine has been used extensively for surgical procedures during pregnancy with no reports of ill effects to mother or fetus, there are no adequate and well-controlled studies in pregnant women of the effect of bupivacaine on the developing fetus. It should therefore be used cautiously during pregnancy other than labour.

Adrenaline (epinephrine) has been given to large numbers of pregnant women and women of child-bearing age without any proven increase in the frequency of malformation or other indirect harmful effects on the fetus having been observed.

The addition of adrenaline (epinephrine) may potentially decrease uterine blood flow and contractility, especially after inadvertent injection into maternal blood vessels.

Adrenaline (epinephrine) may delay the second stage of labour by inhibiting uterine contractions.

Adrenaline (epinephrine)-free solutions should be used during labour for pudendal blocks.

Use in lactation

Bupivacaine passes into breast milk. The amount of bupivacaine appearing in breast milk from a nursing mother receiving parenteral bupivacaine is unlikely to lead to a significant accumulation of the parent drug in the breast-fed infant.

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).

The possibility of an idiosyncratic or allergic reaction in the breast-fed infant from bupivacaine remains to be determined.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Depending on the dosage, local anaesthetics may have a mild effect on mental function and coordination and may temporarily impair locomotion and coordination.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse reactions to bupivacaine are rare in the absence of overdosage, exceptionally rapid absorption or inadvertent intravascular injection. These adverse reactions are similar in character to those observed with other amide-type local anaesthetics and pertain mainly to the central nervous system and the cardiovascular system.

Adverse reactions to bupivacaine are, in general, dose-related and may result from high plasma levels caused by excessive dosage, rapid absorption, delayed elimination, altered metabolism, inadvertent intravascular injection or may result from a hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient.

Serious adverse experiences are generally systemic in nature. Ventricular arrhythmias, ventricular fibrillation, sudden cardiovascular collapse and death have been reported when bupivacaine has been utilised for local anaesthetic procedures that may result in high systemic concentrations of bupivacaine (see Section 4.4 Special Warnings and Precautions for Use).

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

Adverse reactions to adrenaline (epinephrine) are similar to those observed with other sympathomimetics. These may include dizziness, unusual anxiety, nervousness, restlessness, headache, hypertension and tachycardia.

Central nervous system

CNS manifestations are excitatory and/or depressant and may be characterised by light-headedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred vision, diplopia, nausea, vomiting, sensations of heat, cold or numbness, urinary retention, paraesthesia circumoral, paraesthesia, hyperacusis, twitching, tremors, convulsions, unconsciousness, respiratory depression and/or arrest, agitation, numbness of the tongue, difficulty swallowing and slurred speech.

The excitatory manifestations may be very brief or may not occur at all, in which case the first manifestation of toxicity may be drowsiness merging into unconsciousness and respiratory arrest. Drowsiness following administration of bupivacaine is usually an early sign of a high blood level of the drug and may occur as a result of rapid absorption. In unconscious patients, circulatory collapse should be watched as CNS effects may not be apparent as an early manifestation of toxicity may in some cases progress to frank convulsions and ultimately lead to respiratory depression and/or arrest. It is crucial to have resuscitative equipment and anticonvulsant drugs available to manage such patients. (see Section 4.9 Overdose -Treatment of Overdosage).

Cardiovascular

Cardiovascular manifestations following inadvertent intravascular injection are usually depressant and are characterised by bradycardia, hypotension, and cardiovascular collapse, which may lead to cardiac arrest (see Section 4.9 Overdose).

Haemodynamic

Regional anaesthesia may lead to maternal hypotension.

Neurologic

The incidences of adverse reactions associated with the use of local anaesthetics may be related to the total dose of local anaesthetic administered and are also dependent on the particular drug used, the route of administration and the physical status of the patient.

In the practice of caudal or lumbar epidural block, occasional unintentional penetration of the subarachnoid space by the catheter may occur. Subsequent adverse effects may depend partially on the amount of drug administered subdurally.

These may include spinal block of varying magnitude (including total spinal block), hypotension secondary to spinal block, loss of bladder and bowel control and loss of perineal sensation and sexual function. Persistent motor, sensory and/or autonomic (sphincter control) deficit of some lower spinal segments with slow recovery (several months) or incomplete recovery have been reported in rare instances when caudal or lumbar epidural block has been attempted. Backache and headache have also been noted following use of these anaesthetic procedures.

Paresis, paraplegia, neuropathy, peripheral nerve injury and arachnoiditis have been observed.

The effects of systemic overdose and unintentional intravascular injection may involve the central nervous system and/or the cardiovascular system (see Section 4.9 Overdose). Inadvertent subarachnoid injection may lead to CNS depression, respiratory arrest and cardiovascular collapse.

Allergic

Allergic reactions are characterised by cutaneous lesions, urticaria, oedema or anaphylactoid reactions.

Allergy to amide-type local anaesthetics is rare. Sodium metabisulfite, which is included in solutions containing adrenaline (epinephrine), may also cause this type of reaction. If such a reaction occurs, it should be managed by conventional means.

The detection of sensitivity by skin testing is of doubtful value.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Acute emergencies associated with the use of local anaesthetics are generally related to high plasma levels or to unintended subarachnoid injection of the local anaesthetic solution (see Section 4.4 Special Warnings and Precautions for Use and 4.8 Adverse Effects (undesirable effects)).

With accidental intravascular injections of local anaesthetics, the toxic effects will be obvious within 1 - 3 minutes. With overdosage, peak plasma concentrations may not be reached for 20 - 30 minutes, depending on the site of injection and toxic signs will be delayed. Toxic reactions mainly involve the central nervous and cardiovascular systems.

Symptoms of Acute Toxicity

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, lightheadedness, hyperacusis and tinnitus. Visual disturbances and muscular tremors are more serious and precede the onset of generalised convulsions. These signs must not be mistaken for neurotic behaviour.

Unconsciousness and grand mal convulsions may follow. These may last from a few seconds to several minutes. Hypoxia and hypercapnia occur rapidly following convulsions due to increased muscular activity, together with the interference with normal respiration and loss of the airway. In severe cases, apnoea may occur. Acidosis, hyperkalaemia, hypocalcaemia and hypoxia increase and extend the toxic effects of local anaesthetics.

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

Signs of cardiovascular toxicity indicates a more severe situation.
Hypotension, bradycardia, decreased cardiac output, heart block, arrhythmia and even ventricular arrhythmias, ventricular fibrillation and cardiac arrest may occur as a result of high systemic concentrations of local anaesthetics.

Overdosage with adrenaline (epinephrine) produces a rapid rise in blood pressure which may result in cerebrovascular haemorrhage, cardiac arrhythmia leading to ventricular fibrillation and death. Pulmonary oedema may also lead to death because of the peripheral constriction and cardiac stimulation produced.

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 drugs such as benzodiazepines or barbiturates.

Treatment of Overdosage

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

If convulsions occur then immediate attention is required for the maintenance of patent airway and assisted or controlled ventilation with oxygen, via a positive airway pressure delivery system mask. Adequacy of the circulation should then be evaluated, bearing in mind that drugs used to treat convulsions depress the circulation when administered intravenously.

Should convulsions persist despite adequate respiratory support, and if the status of the circulation permits, appropriate anticonvulsant medication such as an ultra-short acting barbiturate (e.g. thiopentone) or a benzodiazepine (e.g. diazepam) may be administered IV. The clinician should be familiar with these anticonvulsant drugs prior to use of local anaesthetics.

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 occurs (hypotension, bradycardia), appropriate treatment with intravenous fluids, vasopressor, inotropic agents and/or lipid emulsion should be considered. Children should be given doses commensurate with age and weight.

If ventricular fibrillation or cardiac arrest occurs, effective cardiovascular resuscitation treatment must be instituted and maintained for a prolonged period if necessary. Optimal oxygenation and ventilation, and circulatory support as well as treatment of acidosis are of vital importance.

To counteract the pressor effects of adrenaline (epinephrine), use rapidly acting vasodilators, for instance nitrates or α-blocking agents.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia)

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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. Bupivacaine is classed as a membrane stabilising agent and is a local anaesthetic of the amide type. Local anaesthetics of the amide type are thought to act within the sodium channels of the nerve membrane.

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

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.

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

Adrenaline (epinephrine) acts on both alpha- and beta-adrenergic receptors of tissue innervated by sympathetic nerves, except for the sweat glands and arteries of the face. It is the most important alpha receptor activator. Adrenaline (epinephrine) stimulates the heart to increase output: raises the systolic blood pressure; lowers diastolic blood pressure; relaxes bronchial spasm and mobilises liver glycogen, resulting in hyperglycaemia and possibly glycosuria.

5.1.1 Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Bupivacaine 0.125%, 0.25%, 0.375% and 0.5% solutions for injection, with or without adrenaline (epinephrine), are available in other brands. Pharmacokinetic information obtained using bupivacaine 0.125%, 0.25%, 0.375% and 0.5% solutions for injection, with or without adrenaline (epinephrine), are also included in the following sub-sections for prescriber information.

Bupivacaine is a long acting, amide-type local anaesthetic chemically related to lidocaine (lignocaine) and mepivacaine. It is approximately four times as potent as lidocaine (lignocaine).

In concentrations of 5 mg/mL it has a long duration of action, from 2 - 5 hours following a single epidural injection and up to 12 hours after peripheral nerve blocks. The onset of the blockade is slower than with lidocaine (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. The addition of a vasoconstrictor such as adrenaline (epinephrine) may decrease the rate of absorption and prolong the duration of action. After injection of bupivacaine 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 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 concentrations. Epidural and major plexus blocks are intermediate. In children rapid absorption (plasma concentrations are in the order of 1 - 1.5 mg/L after a dose of 3 mg/kg) is seen with caudal block. Absorption may be slowed by the addition of adrenaline (epinephrine).

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 hours and an intermediate hepatic extraction ratio of 0.40 following experimental IV administration in adults. The terminal elimination half-life is prolonged in the newborn to approximately 8 hours. In children aged over 3 months the elimination half-life is similar to that in adults. Bupivacaine is mainly bound to α1-acid glycoprotein in plasma with a plasma binding of 96%.

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 α1-acid glycoprotein, which occurs postoperatively after major surgery, may cause an increase in the total plasma concentration of bupivacaine. The level of free drug will remain the same. This explains why total plasma concentrations above the apparent toxic threshold level of 2.6 - 3.0 mg/L are apparently well tolerated in this situation.

Bupivacaine is excreted in the urine principally as metabolites with about 6% as unchanged drug. 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, presence or absence of adrenaline (epinephrine) in the solution and certain concomitant medication.

5.3 PRECLINICAL SAFETY DATA

5.3.1 Genotoxicity

Formal studies of mutagenic potential have not been carried out.

5.3.2 Carcinogenicity

Long-term studies in animals of most local anaesthetics, including bupivacaine, to evaluate the carcinogenic potential have not been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Bupivacaine 0.5% with Adrenaline 1:200,000 Phebra contains sodium chloride, sodium metabisulfite, hydrochloric acid (for pH adjustment) and water for injections.

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 between Bupivacaine 0.5% with Adrenaline 1:200,000 Phebra and metal surfaces, such as metal bowls, cannulae and syringes with metal parts.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG)[1]. The expiry date can be found on the packaging.

Bupivacaine 0.5% with Adrenaline 1:200,000 Phebra contains no antimicrobial agent and should be used only once and any residue discarded.

Solutions showing discolouration and unused portions of solutions from single dose vials should be discarded.

Bupivacaine 0.5% with Adrenaline 1:200,000 Phebra should not be reautoclaved. Surface sterilisation using pure, undiluted isopropyl alcohol (91%) or 70% ethanol maybe carried out if desired. Soaking of any Bupivacaine 0.5% with Adrenaline 1:200,000 Phebra presentation is not recommended.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Bupivacaine 0.5% with Adrenaline 1:200,000 Phebra should be stored below 25˚C and protected from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Bupivacaine 0.5% with Adrenaline 1:200,000 Phebra is supplied in a sterile theatre pack which contains one clear glass 20 mL single dose vial with a grey chlorobutyl rubber stopper, a plastic cap and an aluminium Flip-Off Tear-Off seal. Each carton contains 5 sterile theatre packs, each containing 1 x 20 mL single dose vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Single use only. Discard any unused content.

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Bupivacaine hydrochloride is a white or almost white, crystalline powder or colourless crystals. It is soluble in water and freely soluble in ethanol (96%). Bupivacaine has a pKa of 8.09 and is more lipid soluble than lidocaine (lignocaine).

[1] AUST R 373819

The chemical name for bupivacaine hydrochloride (as monohydrate) is (2*RS*)-1-Butyl-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide hydrochloride monohydrate.

Bupivacaine hydrochloride (as monohydrate) has the chemical formula $C_{18}H_{29}ClN_2O,H_2O$ and molecular weight value 342.9.

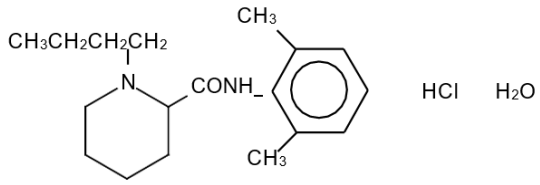
Adrenaline (epinephrine) acid tartrate appears as a white to greyish-white, crystalline powder that is freely soluble in water and slightly soluble in ethanol (96%) and methanol.

The chemical name for adrenaline (epinephrine) is (1*R*)-1-(3,4-Dihydroxyphenyl)-2-(methylamino)ethanol hydrogen (2 *R*,3 *R*)-2,3-dihydroxybutanedioate.

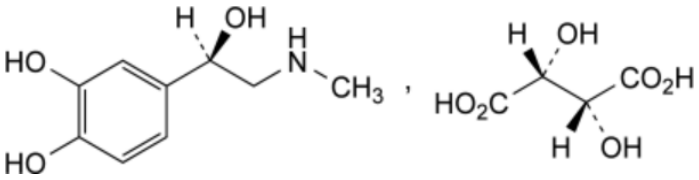
Adrenaline (epinephrine) acid tartrate has the chemical formula $C_{13}H_{19}NO_9$ and a molecular weight of 333.3.

Chemical structure

The chemical structure of bupivacaine hydrochloride (as monohydrate) is



The chemical structure of adrenaline (epinephrine) acid tartrate is:



CAS number

The CAS number for bupivacaine hydrochloride monohydrate is 73360-54-0.

The CAS number for adrenaline (epinephrine) acid tartrate is 51-42-3.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine).

8 SPONSOR

Phebra[2] Pty Ltd, 19 Orion Road, Lane Cove West, NSW 2066, Australia.

Ph 1800 720 020

[2] Phebra and the Phi symbol are trademarks of Phebra Pty Ltd, 19 Orion Road, Lane Cove West, NSW 2066, Australia.

9 DATE OF FIRST APPROVAL

07 October 2022

10 DATE OF REVISION

Not applicable

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
NA	New Product Information.