Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bupivacaine Amneal 5mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 5 mg of bupivacaine hydrochloride monohydrate
Each vial with 10 ml solution contains 50 mg of bupivacaine hydrochloride monohydrate.
Each vial with 20 ml solution contains 100 mg of bupivacaine hydrochloride monohydrate.

Excipient with known effect:
Each ml of the solution contains 3.15 mg of sodium.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.
A clear, colourless, aqueous, sterile solution.
pH of the solution is between 4.0 and 6.5 and osmolarity is 290 mOsmol/l.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the production of local anaesthesia by peripheral nerve block(s) and central neural block (caudal or epidural), that is, for specialist use in situations where prolonged anaesthesia is required. Bupivacaine-Amneal is also indicated for the relief of labour pain.

- Surgical anaesthesia in adults and children above 12 years of age
- Acute pain management in adults, infants and children above 1 year of age.

4.2 Posology and method of administration

Posology

Adults and children above 12 years of age

The dosage varies and depends upon the area to be anaesthetised, the vascularity of the tissues, the number of neuronal segments to be blocked, individual tolerance and the technique of anaesthesia used. The lowest dosage needed to provide effective anaesthesia should be administered. For most indications, the duration of anaesthesia with Bupivacaine solutions is such that a single dose is sufficient.

The maximum dosage must be determined by evaluating the size and physical status of the patient and considering the usual rate of systemic absorption from a particular injection site. Experience to date indicates a single dose of up to 150 mg bupivacaine hydrochloride monohydrate. Doses of up to 50 mg 2-hourly may subsequently be used. A maximum dose of 2 mg/kg should not be exceeded in any four-hour period.

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.

The dosages in the following table are recommended as a guide for use in the average adult. Individual variations in onset and duration occur. For young, elderly or debilitated patients, these doses should be reduced.

Table 1 Dosage recommendations for adults

	Conc mg/ml	Volume ml	Dose mg	Onset min	Duration hours
SURGICAL ANAESTHESIA					
Lumbar Epidural Administration [1)]					
Surgery	5.0	15-30	75-150	15-30	2-3
Lumbar Epidural Administration [1)]					
Caesarean Section	5.0	15-30	75-150	15-30	2-3
Thoracic Epidural Administration [1)]					
Surgery	2.5	5-15	12.5-37.5	10-15	1.5-2
	5.0	5-10	25-50	10-15	2-3
Caudal Epidural Block [1)]					
	2.5	20-30	50-75	20-30	1-2
	5.0	20-30	100-150	15-30	2-3
Major Nerve Block [2)]					
(eg, brachial plexus, femoral, sciatic)	5.0	10-30	50-150	15-30	4-8
Field block					
(eg, minor nerve blocks and infiltration)	2.5	<60	<150	1-3	3-4
	5.0	≤30	≤150	1-10	3-8
ACUTE PAIN MANAGEMENT					
Lumbar Epidural Administration					
Intermittent injections [3)] (e.g. post-operative pain relief)	2.5	6-15; minimum interval 30 minutes	15-37.5; minimum interval 30 minutes	2-5	1-2

Continuous infusion [4]	1.25	10-15/h	12.5-18.8/h	-	-
	2.5	5-7.5/h	12.5-18.8/h	-	-
Continuous infusion, labour pain relief [4]	1.25	5-10/h	6.25-12.5/h	-	-
Thoracic Epidural Administration					
Continuous infusion	1.25	5-10/h	6.3-12.5/h	-	-
	2.5	4-7.5/h	10-18.8/h	-	-
Intra-Articular Block [5]					
(eg, following knee arthroscopy)	2.5	≤40	≤100	5-10	2-4 h after wash out
Field Block					
(eg, minor nerve blocks and infiltration)	2.5	≤60	≤150	1-3	3-4

Notes:

1. Dose includes test dose.
2. The dose for a major nerve block must be adjusted according to site of administration and patient status. Interscalene and brachial plexus blocks may be associated with a higher frequency of serious adverse reactions, regardless of the local anaesthetic used, see also section 4.4.
3. In total ≤500 mg/24 h.
4. This solution is often used for epidural administration in combination with a suitable opioid for pain management. In total ≤500 mg/24 h.
5. If additional bupivacaine is used by any other techniques in the same patient, an overall dose limit of 150 mg should not be exceeded.

In general, surgical anaesthesia (e.g. epidural administration) requires the use of higher concentrations and doses. When a less intense block is required, the use of a lower concentration is indicated. The volume of medicinal product used will affect the extent of spread of anaesthesia.

In order to avoid intravascular injection, aspiration should be repeated prior to and during administration of the main dose, which should be injected slowly or in incremental doses, at a rate of 25 - 50 mg/min, while closely observing the patient's vital functions and maintaining verbal contact. When an epidural dose is to be injected, a preceding test dose of 3 - 5 ml bupivacaine containing adrenaline (epinephrine) is recommended.

An inadvertent intravascular injection may be recognised by a temporary increase in heart rate and an accidental intrathecal injection by signs of a spinal block. If toxic symptoms occur, the injection should be stopped immediately.

Paediatric patients 1 to 12 years of age

Paediatric regional anaesthetic procedures should be performed by qualified clinicians who are familiar with this population and the technique.

The doses in the table should be regarded as guidelines for use in paediatrics. Individual variations occur. In children with a high body weight a gradual reduction of the dosage is often necessary and should be based on the ideal body weight. Standard textbooks should be consulted for factors affecting specific block techniques and for individual patient requirements.

The lowest dose required for adequate analgesia should be used.

Table 2 Dosage recommendations for children 1 to 12 years of age

	Conc. mg/ml	Volume ml/kg	Dose mg/kg	Onset min	Duration hours
Acute Pain Management (pre- and postoperative)					
Caudal Epidural Administration	2.5	0.6-0.8	1.5-2	20-30	2-6
Lumbar Epidural Administration	2.5	0.6-0.8	1.5-2	20-30	2-6
Thoracic Epidural Administration[b)]	2.5	0.6-0.8	1.5-2	20-30	2-6
Field Block (e.g. minor nerve blocks and infiltration)	2.5		0.5-2.0		
	5.0		0.5-2.0		
Peripheral Nerve Blocks (e.g ilioinguinal – iliohypogastric)	2.5		0.5-2.0	a)	
	5.0		0.5-2.0	b)	

a) The onset and duration of peripheral nerve blocks depend on the type of block and the dose administered.
b) Thoracic epidural blocks need to be given by incremental dosage until the desired level of anaesthesia is achieved.

In children the dosage should be calculated on a weight basis up to 2 mg/kg.

In order to avoid intravascular injection, aspiration should be repeated prior to and during administration of the main dose. This should be injected slowly in incremental doses, particularly in the lumbar and thoracic epidural routes, constantly and closely observing the patient's vital functions.

Peritonsillar infiltration has been performed in children above 2 years of age with bupivacaine 2.5 mg/ml at a dose of 7.5 - 12.5mg per tonsil.

Ilioinguinal-iliohypogastric blocks have been performed in children aged 1 year or older with bupivacaine 2.5 mg/ml at a dose of 0.1 - 0.5 ml/kg equivalent to 0.25 - 1.25 mg/kg. Children aged 5 years or older have received bupivacaine 5 mg/ml at a dose of 1.25-2 mg/kg.

For penile blocks bupivacaine 5 mg/ml has been used at total doses of 0.2 - 0.5 ml/kg equivalent to 1 - 2.5 mg/kg.

The safety and efficacy of Bupivacaine-Amneal in children < 1 year of age have not been established. Only limited data are available.

Safety and efficacy of intermittent epidural bolus injection or continuous infusion have not been established. Only limited data is available.

For doses not realisable/practicable with this strength other strengths of this medicinal product are available.

Method of administration

For single use only. The solution / dilution should be inspected visually prior to use.
Only clear solutions practically free from particles should be used.

4.3 Contraindications

Bupivacaine-Amneal is contra-indicated in patients with hypersensitivity to bupivacaine hydrochloride monohydrate, local anaesthetic agents of the amide type or to any of the other excipients listed in section 6.1.

Solutions of bupivacaine hydrochloride monohydrate are contra-indicated for intravenous regional anaesthesia (Bier's-block) and obstetrical paracervical block.

The following general contraindications should be taken into consideration in case of intrathecal and / or epidural anaesthesia.

- active acute diseases of the Central Nervous System such as meningitis, tumours, poliomyelitis and intracranial haemorrhage.
- Spinal stenosis and active disease of the spinal column (for example: spondylitis, tuberculosis, tumours) or recent traumatic events (for example fractures)
- Septicaemia.
- pernicious anaemia associated with sub-acute degeneration of the bone marrow
- pyogenic infection of the skin in the site of injection or in the surrounding area
- cardiogenic or hypovolaemic shock
- coagulation disorders or current anticoagulant treatments.

Epidural anaesthesia, regardless of the local anaesthetic used, has its own contra-indications which include:

Active disease of the central nervous system such as meningitis, poliomyelitis, intracranial haemorrhage, sub-acute combined degeneration of the cord due to pernicious anaemia and cerebral and spinal tumours; tuberculosis of the spine; pyogenic infection of the skin at or adjacent to the site of lumbar puncture; cardiogenic or hypovolaemic shock; coagulation disorders or ongoing anticoagulation treatment.

4.4 Special warnings and precautions for use

General precautions and risk of bupivacaine use:

There have been reports of cardiac arrest during the use of bupivacaine for epidural anaesthesia or peripheral nerve blockade where resuscitative efforts have been difficult, and were required to be prolonged before the patient responded. However, in some instances resuscitation has proven impossible despite apparently adequate preparation and appropriate management.

Like all local anaesthetic medicinal products, 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 medicinal product. 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.

Major peripheral nerve blocks may require the administration of a large volume of local anaesthetic in areas of high vascularity, often close to large vessels where there is an increased risk of intravascular injection and/or systemic absorption. This may lead to high plasma concentrations.

Before any nerve block is attempted, intravenous access for resuscitation purposes should be established. Clinicians should have received adequate and appropriate training in the procedure to be performed and should be familiar with the diagnosis and treatment of side effects, systemic toxicity or other complications (see section 4.9).

Adequate resuscitation equipment should be available whenever local or general anaesthesia is administered. The clinician responsible should take the necessary precautions to avoid intravascular injection (see section 4.2).

Overdosage or accidental intravenous injection may give rise to toxic reactions.

Injection of repeated doses of bupivacaine hydrochloride may cause significant increases in blood levels with each repeated dose due to slow accumulation of the medicinal product. Tolerance varies with the status of the patient.

Debilitated, elderly or acutely ill patients should be given reduced doses commensurate with their physical status.

Patients at risk, and Risk associated with certain anaesthesia techniques:

Patients treated with anti-arrhythmic medicinal products class III (e.g. amiodarone) should be under close surveillance and ECG monitoring, since cardiac effects may be additive.

Only in rare cases have amide local anaesthetics been associated with allergic reactions (in most severe instances anaphylactic shock).

Patients allergic to ester-type local anaesthetic medicinal products (procaine, tetracaine, benzocaine, etc.) have not shown cross-sensitivity to agents of the amide type such as bupivacaine.

Local anaesthetics should be used with caution for epidural anaesthesia in patients with impaired cardiovascular function since they may be less able to compensate for functional changes associated with the prolongation of A-V conduction produced by these medicinal products.

Since bupivacaine is metabolised in the liver, it should be used cautiously in patients with liver disease or with reduced liver blood flow.

The physiological effects generated by a central neural blockade are more pronounced in the presence of hypotension. Patients with hypovolaemia due to any cause can develop sudden and severe hypotension during epidural anaesthesia. Epidural anaesthesia should therefore be avoided or used with caution in patients with untreated hypovolaemia or significantly impaired venous return.

Epidural anaesthesia with any local anaesthetic can cause hypotension and bradycardia which should be anticipated and appropriate precautions taken. These may include pre-loading the circulation with crystalloid or colloid solution. If hypotension develops it should be treated with a vasopressor such as ephedrine 10-15 mg intravenously. Severe hypotension may result from hypovolaemia due to haemorrhage or dehydration, or aorto-caval occlusion in patients with massive ascites, large abdominal tumours or late pregnancy. Marked hypotension should be avoided in patients with cardiac decompensation.

Patients with hypovolaemia due to any cause can develop sudden and severe hypotension during epidural anaesthesia.

Epidural anaesthesia can cause intercostal paralysis and patients with pleural effusions may suffer respiratory embarrassment. Septicaemia can increase the risk of intraspinal abscess formation in the postoperative period.

Small doses of local anaesthetics injected into the head and neck, including retrobulbar, dental and stellate ganglion blocks, may produce systemic toxicity due to inadvertent intra-arterial injection.

Retrobulbar injections may very rarely reach the cranial subarachnoid space causing serious/severe reactions, including temporary blindness, cardiovascular collapse, apnoea, convulsions.

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 and/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.

Particular caution is to be taken in case of injecting local anaesthetics into inflamed or infected areas.

This medicinal product contains 0.14 mmol (3.15 mg) sodium per ml. To be taken into consideration by patients on a controlled sodium diet.

Paediatric population

The safety and efficacy of Bupivacaine-Amneal in children < 1 year of age have not been established. Only limited data are available.

The use of bupivacaine for intra-articular block in children 1 to 12 years of age has not been documented.

The use of bupivacaine for major nerve block in children 1 to 12 years of age has not been documented.

For Epidural anaesthesia children should be given incremental doses commensurate with their age and weight as especially epidural anaesthesia at a thoracic level may result in severe hypotension and respiratory impairment.

4.5 Interaction with other medicinal products and other forms of interaction

Bupivacaine should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics, e.g. certain anti-arrhythmics, such as lidocaine and mexiletine, since the systemic toxic effects are additive.

Specific interaction studies with bupivacaine and anti-arrhythmic medicinal product class III (e.g. amiodarone) have not been performed, but caution should be advised, (see also Section 4.4).

Cases of severe hypotension are reported when clonidine was mixed with local anaesthetics like bupivacaine in blocks. Combinations with ketamine may cause neurotoxicity.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are limited amount of data from the use of bupivacaine in human pregnancy. Animal studies have shown decreased pup survival and embryotoxic effects (see section 5.3). The potential risk for human is unknown. Bupivacaine injection should therefore not be given in pregnancy unless the benefits are considered to outweigh the risks.

Bupivacaine solutions are contraindicated for use in paracervical block in obstetrics, because foetal bradycardia may occur following paracervical block (see section 4.3).

Breast-feeding
Bupivacaine enters the mother's milk, but in such small quantities that there is no risk of affecting the child at therapeutic dose levels.

4.7 Effects on ability to drive and use machines

Besides the direct anaesthetic effect, local anaesthetics may have a very mild effect on mental function and co-ordination even in the absence of overt CNS toxicity, and may temporarily impair locomotion and alertness.

4.8 Undesirable effects

Serious systemic adverse reactions are rare, but may occur in connection with overdosage (see section 4.9) or unintentional intravascular injection.

Bupivacaine causes systemic toxicity similar to that observed with other local anaesthetic agents. It is caused by high plasma concentrations as a result of excessive dosage, rapid absorption or, most commonly, inadvertent intravascular injection. Pronounced acidosis or hypoxia may increase the risk and severity of toxic reactions. Such reactions involve the central nervous system (CNS) and the cardiovascular system. CNS reactions are characterised by numbness of the tongue, light-headedness, dizziness, blurred vision and muscle twitch, followed by drowsiness, convulsions,

unconsciousness and possibly respiratory arrest.

Cardiovascular reactions are related to depression of the conduction system of the heart and myocardium leading to decreased cardiac output, heart block, hypotension, bradycardia and sometimes ventricular arrhythmias, including ventricular tachycardia, ventricular fibrillation and cardiac arrest. Usually these will be preceded or accompanied by major CNS toxicity, i.e. convulsions, but in rare cases cardiac arrest has occurred without prodromal CNS effects.

Epidural anaesthesia itself can cause adverse reactions regardless of the local anaesthetic agent used. These include hypotension and bradycardia due to sympathetic blockade and/or vasovagal fainting.

In severe cases cardiac arrest may occur.

Accidental sub-arachnoid injection can lead to very high spinal anaesthesia possibly with apnoea and severe hypotension.

Neurological damage is a rare but well recognised consequence of regional and particularly epidural and spinal anaesthesia. It may be due to several causes, e.g. direct injury to the spinal cord or spinal nerves, anterior spinal artery syndrome, injection of an irritant substance, or an injection of a non-sterile solution. These may result in localised areas of paraesthesia or anaesthesia, motor weakness, loss of sphincter control and paraplegia. Occasionally these are permanent.

Hepatic dysfunction, with reversible increases of SGOT, SGPT, alkaline phosphates and bilirubin, has been observed following repeated injections or long-term infusions of bupivacaine. If signs of hepatic dysfunction are observed during treatment with bupivacaine, the medicinal product should be discontinued.

Adverse reactions are presented according to the MedDRA system organ classes and MedDRA frequency convention:

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1 /1,000 to < 1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Very common	Vascular disorders	Hypotension
	Gastrointestinal disorders	Nausea
Common	Nervous system disorders	Paraesthesia, dizziness
	Cardiac disorders	Bradycardia
	Vascular disorders	Hypertension
	Gastrointestinal disorders	Vomiting
	Renal and urinary disorders	Urinary retention
Uncommon	Nervous system disorders	Signs and symptoms of CNS toxicity (convulsions, circumoral paresthesia, numbness of the tongue, hyperacusis, blurred vision, unconsciousness, tremor, light headedness, tinnitus, dysarthria).
Rare	Immune system disorders	Allergic reactions, anaphylactic reactions/shock
	Nervous system disorders	Neuropathy, periphery nerve injury, arachnoiditis
	Eye disorders	Diplopia
	Cardiac disorders	Cardiac arrest, cardiac arrhythmia
	Respiratory disorders	Respiratory depression

Paediatric population
*Adverse drug reactions in children are similar to those in adults, however, i*n children, early signs of local anaesthetic toxicity may be difficult to detect in cases where the block is given during sedation or general 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 national reporting system

Ireland
Pharmacovigilance Section
Irish Medicines Board
Kevin O'Malley House
Earlsfort Centre
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.imb.ie
e-mail: imbpharmacovigilance@imb.ie

4.9 Overdose

Accidental intravascular injections of local anaesthetics may cause immediate (within seconds to a few minutes) systemic toxic reactions. In the event of overdose, systemic toxicity appears later (15 - 60 minutes after injection) due to the slower increase in local anaesthetic blood concentration.

Acute systemic toxicity

Systemic toxic reactions primarily involve the central nervous system (CNS) and the cardiovascular system. Such reactions are caused by high blood concentrations of a local anaesthetic, which may appear due to (accidental) intravascular injection, overdose or exceptionally rapid absorption from highly vascularised areas (see section 4.4). CNS reactions are similar for all amide local anaesthetics, while cardiac reactions are more dependent on the medicinal product, both quantitatively and qualitatively. Signs of toxicity in the central nervous system generally precede cardiovascular toxic effects, unless the patient is receiving a general anaesthetic or is heavily sedated with medicinal products such as benzodiazepine or barbiturate.

Central nervous system toxicity is a graded response with symptoms and signs of escalating severity. The first symptoms are usually, circumoral paraesthesia, numbness of the tongue, light-headedness, hyperacusis, tinnitus and visual disturbances. Dysarthria, muscular twitching or 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, 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 respiration and possible loss of functional airways. 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 medicinal product from the central nervous system and subsequent metabolism and excretion. Recovery may be rapid unless large amounts of the medicinal product have been injected.

Cardiovascular system toxicity may be seen in severe cases and is generally preceded by signs of toxicity in the central nervous system. In patients under heavy sedation or receiving a general anaesthetic, prodromal CNS symptoms may be absent. Hypotension, bradycardia, arrhythmia and even cardiac arrest may occur as a result of high systemic concentrations of local anaesthetics, but in rare cases cardiac arrest has occurred without prodromal CNS effects.

In children, early signs of local anaesthetic toxicity may be difficult to detect in cases where the block is given during

general anaesthesia.

Treatment of acute toxicity

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

Treatment of a patient with systemic toxicity consists of arresting convulsions and ensuring adequate ventilation with oxygen, if necessary by assisted or controlled ventilation (respiration). If convulsions occur they must be treated promptly by intravenous injection of thiopental 100 - 200 mg or diazepam 5 - 10 mg.

Prolonged convulsions may jeopardise the patient's ventilation and oxygenation. If so, injection of a muscle relaxant (e.g. succinylcholine 1 mg/kg bw) will facilitate ventilation, and oxygenation can be controlled. Early endotracheal intubation must be considered in such situations.

Once convulsions have been controlled and adequate ventilation of the lungs ensured, no other treatment is generally required. If hypotension is present, however, a vasopressor, preferably one with inotropic activity, e.g. ephedrine 15 - 30 mg, should be given intravenously.

If circulatory arrest should occur, immediate cardiopulmonary resuscitation should be instituted. Optimal oxygenation and ventilation and circulatory support as well as treatment of acidosis are of vital importance.

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

Should cardiac arrest occur, a successful outcome may require prolonged resuscitative efforts.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anaesthetics, local; Amides ATC code: NOlBBOl.

Bupivacaine is a potent amide local anaesthetic with a prolonged duration of action. It affects sensory nerves more than motor nerves and is ideal for producing analgesia without motor blockade.

5.2 Pharmacokinetic properties

In adults, the terminal half-life of bupivacaine is 3.5 hours. The maximum blood concentration varies with the site of injection and is highest after intercostal nerve blockade.

Total dose, rather than concentration, is an important determinant of peak blood levels.

Bupivacaine is biodegraded in the liver and only 6% is excreted unchanged in the urine.

Paediatric population
In children the pharmacokinetics is similar to that in adults.

5.3 Preclinical safety data

Based on conventional studies of safety pharmacology, acute and subchronic toxicity, non-clinical data reveal no special hazard other than those already reported elsewhere in this document.

The mutagenic and carcinogenic potential of bupivacaine has not been determined.
Bupivacaine crosses the placenta. In reproduction toxicity studies, decreased survival of the offspring of rats and embryolethality was noted in rabbits at bupivacaine doses, which were five- or nine-fold the maximum recommended

daily dose in humans. A study in rhesus monkeys suggested altered postnatal behaviour following exposition to bupivacaine at birth.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
0.4% sodium hydroxide (for pH adjustment)
0.85% hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

Bupivacaine may precipitate if diluted with alkaline solutions and should not be diluted or co-administered with sodium bicarbonate injections. This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years

After first opening: to be used immediately and discard any unused solution.

After dilution: Chemical and physical in use stability has been demonstrated for 36 hours at 25º C.

From a microbiological point of view the product should be used immediately.

6.4 Special precautions for storage

Store below 30°C. Do not refrigerate or freeze.

For storage conditions after dilution and first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10 ml type I clear glass vial with bromobutyl rubber closure
20 ml type I clear glass vial with bromobutyl rubber closure

Pack sizes:
5 X 10 ml Solution for Injection
1 X 20 ml Solution for Injection
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Bupivacaine is compatible when mixed with sodium chloride 9 mg/ml (0.9%) solution for injection, Ringer Lactate Solution and Sufentanil Citrate 50 µg/ml.

7 MARKETING AUTHORISATION HOLDER

Amneal Pharma Europe Limited
70 Sir John Rogerson's Quay
Dublin 2
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1897/001/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st April 2011

10 DATE OF REVISION OF THE TEXT

May 2014