BUPIVACAINE 0.25%W/V SOLUTION FOR INJECTION
PL 20910/0008

BUPIVACAINE 0.5%W/V SOLUTION FOR INJECTION
PL 20910/0009

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LAY SUMMARY

The MHRA granted Taro Pharmaceuticals (Ireland) Limited Marketing Authorisations (licences) for the medicinal products Bupivacaine 0.25%w/v Solution for Injection (PL 20910/0008) and Bupivacaine 0.5%w/v Solution for Injection (PL 20910/0000). These are prescription-only medicines (POM) are used as local anaesthetics during surgical operations, such as obstetric operations such as caesarean section; relief of acute pain, including labour pain or pain after an operation; or in the diagnosis and treatment of chronic pain.

Bupivacaine Solution for Injection contains the active ingredient bupivacaine hydrochloride, which belongs to a group of medicine called amide-type local anaesthetics.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Bupivacaine 0.25%w/v Solution for Injection and Bupivacaine 0.5%w/v Solution for Injection outweigh the risks; hence Marketing Authorisations have been granted.

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PL 20910/0009

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Bupivacaine 0.25%w/v Solution for Injection (PL 20910/0008) and Bupivacaine 0.5%w/v Solution for Injection on 18th April 2007. The products are prescription-only medicines.

These are two strengths of Bupivacaine, submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, as amended and are generic medicinal products of the original products Marcain Polyamp Steripack 0.25% & 0.50% authorised to AstraZeneca UK Ltd in Ireland in September 1988. The reference medicinal products in the UK are Marcain Polyamp Steripack (PL 17901/0144-0145) authorised to AstraZeneca UK Limited in June 2002 following a change of ownership from Astra Pharmaceuticals Limited (PL 00017/0305 & 0307) authorised in April 1993; therefore the 10-year period of data exclusivity has expired.

The products contain the active ingredient bupivacaine hydrochloride (equivalent to anhydrous bupivacaine hydrochloride 2.5mg/ml and 5mg/ml). 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.

Bupivacaine 0.25%w/v & 0.5%w/v Solution for Injection production of local anaesthesia by percutaneous infiltration, peripheral nerve block(s) and central neural block (caudal or epidural), that is, for specialist use in situations where prolonged anaesthesia is required. Because sensory block is more marked than motor block, bupivacaine is especially useful in the relief of pain, e.g. during labour.

These applications were submitted at the same time and all sections of this Scientific Discussion refer to both products.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Bupivacaine hydrochloride

INN: Bupivacaine hydrochloride
Chemical Name: (2*RS*)-1-Butyl-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide hydrochloride monohydrate

Molecular formula: $C_{18}H_{29}ClN_2O$, H_2O
Molecular weight: 342.9

Physical form: White or almost white powder
Solubility: Very slightly soluble in water, soluble in methylene chloride, sparingly soluble in alcohol and methanol. It dissolves in dilute solutions of alkali hydroxides.

Polymorphism: Bupivacaine hydrochloride is not known to exhibit polymorphism.

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active bupivacaine hydrochloride is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the finished product manufacturer during validation studies of the active substance.

Appropriate stability data have been generated supporting a retest period of 60 months, when stored in a double polyethylene (PE) bag inside a fibre drum.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely sodium chloride, sodium hydroxide 10% and water for injection. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeial monograph. Satisfactory certificates of analysis have been provided for all excipients.

None of the excipients used contain material of animal or human origin. There were no novel excipients used and no overages.

Manufacture

A detailed description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on three batches of each strength. The results are satisfactory.

Finished product specification
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Bioavailability, bioequivalence
Since this product is for parenteral administration as intravenous infusion/injection, no bioavailability/bioequivalence studies are required.

Container Closure System
The product is presented in 10 ml polypropylene ampoules. The ampoules are hermetically sealed and are tamper proof and the plastic is inert in respect to reaction with the product. Specifications and certificates of analysis for all packaging types used have been provided. These are satisfactory. The product is packaged in pack sizes of 20 ampoules.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set, which is satisfactory. Storage conditions are “Do not store above 25 degrees” and “Do not refrigerate or freeze”.

Summary of Product Characteristics (SPC)
This is satisfactory.

Labels
These are satisfactory.

Patient Information Leaflet
This is satisfactory. A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for an application of this type.

CLINICAL ASSESSMENT

INTRODUCTION
Bupivacaine is a successful long acting amide type anaesthetic agent well established for use in the requested indication. It has been used all over the world for many years. It was synthesised for the first time in Sweden in 1957. It was first used in Scandinavia, Japan and Germany. The FDA registered the drug in 1973. Currently, a number of UK Marketing Authorisations are granted for generic equivalents.

INDICATIONS
Bupivacaine Injection BP 0.25%w/v and 0.5%w/v are used for the production of local anaesthesia by percutaneous infiltration, peripheral nerve block(s) and central neural block (caudal or epidural), that is, for specialist use in situations where prolonged anaesthesia is required. Because sensory nerve block is more marked than motor block, bupivacaine is especially useful in the relief of pain, e.g. during labour.

The above is essentially the same as the SPC text for the licensed indications of the UK reference product and is satisfactory.

DOSE & DOSE SCHEDULE

The proposed SPC text is essentially the same as that for the UK reference product and is satisfactory.

CLINICAL PHARMACOLOGY

No new data are submitted and none are required for this type of application. No bioequivalence study is required. In accordance with Par.5.1.6 of the note for guidance on Bioavailability and Bioequivalence issued by the CPMP (CPMP/EWP/QWP/1401/98): “The applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous solution containing the same active substance in the same concentration as the currently authorised product. In the case of other parenteral routes (IM,SC), if the product is of the same type of solution, contains the same concentration of the same active substance and the same of comparable excipients as the medicinal product currently approved, then bioequivalence testing is not required.”

EFFICACY
No new data are submitted and none are required for this type of application.

SAFETY
No new data are submitted and none are required for this type of application.

EXPERT REPORTS
A satisfactory expert report is provided by an appropriately qualified individual.

PATIENT INFORMATION LEAFLET (PIL)
The PIL is in line with the SPC, well worded and laid out, and is satisfactory.

LABELLING
The labels are satisfactory.

APPLICATION FORM (MAA)
The MAA is medically satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
The SPC is essentially identical to that licensed for the UK reference product and is satisfactory.

DISCUSSION
The dossier submitted by the applicant is sufficient to establish efficacy and safety in the requested indications. The SPC and PIL are satisfactory.

MEDICAL CONCLUSION
There are no medical objections to the granting of a product licence for this preparation.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Bupivacaine 0.25% w/v & 0.5% w/v Solution for Injection are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

No formal data on clinical efficacy or safety was presented for these applications and none were required.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that of the original products Marcain Polyamp Steripack 0.25% & 0.50%.

RISK BENEFIT ASSESSMENT

The quality of these products is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with bupivacaine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

BUPIVACAINE 0.25%W/V SOLUTION FOR INJECTION
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BUPIVACAINE 0.5%W/V SOLUTION FOR INJECTION
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STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation applications on 26th October 2005.
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 10th November 2005.
3	Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 14th February 2006, 13th July 2006, and 24th October 2006.
4	The applicant responded to the MHRA's requests, providing further information on 08th May 2006, 22nd August 2006, and 08th November 2006 for the quality sections.
5	The applications were determined on 18th April 2007.

BUPIVACAINE 0.25%W/V SOLUTION FOR INJECTION
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BUPIVACAINE 0.5%W/V SOLUTION FOR INJECTION
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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome
15/12/2007	Type II Medical variation	To amend the PSUR cycle from the standard to 3 yearly.	Approved-20/12/2007

BUPIVACAINE 0.25%W/V SOLUTION FOR INJECTION
PL 20910/0008
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Bupivacaine 0.25%w/v solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains bupivacaine hydrochloride 2.64 mg equivalent to anhydrous bupivacaine hydrochloride 2.5 mg.
Each 10 ml contains bupivacaine hydrochloride 26.4 mg equivalent to anhydrous bupivacaine hydrochloride 25 mg.

The product contains sodium chloride.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection
Clear, colourless or almost colourless solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Bupivacaine 0.25%w/v and 0.5%w/v solution for injection are used for the production of local anaesthesia by percutaneous infiltration, peripheral nerve block(s) and central neural block (caudal or epidural), that is, for specialist use in situations where prolonged anaesthesia is required. Because sensory nerve block is more marked than motor block, bupivacaine is especially useful in the relief of pain, e.g. during labour.

A list of indications and the suggested dose and strength of solution appropriate for each are shown in the table below.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

The utmost care should be taken to prevent an accidental intravascular injection, always including careful aspiration. For epidural anaesthesia, a test dose of 3-5 ml of bupivacaine containing adrenaline should be administered, since an intravascular injection of adrenaline will be quickly recognised by an increase in heart rate

Verbal contact and repeated measurement of heart rate should be maintained throughout a period of 5 minutes following the test dose. Aspiration should be repeated prior to administration of the total dose. The main dose should be injected slowly, 25-50 mg/min, in incremental doses under constant contact with the patient. If mild toxic symptoms occur, the injection should be stopped immediately.

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 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. Doses of up to 50 mg 2-hourly may subsequently be used. A total dose of up to 500 mg bupivacaine over 24 hours, which does not include the initial bolus dose, has been used routinely for many

years without reports of toxicity. The dosages in the following table are recommended as a guide for use in the average adult. For young, elderly or debilitated patients, these doses should be reduced.

TYPE OF BLOCK	% CONC.	EACH DOSE		MOTOR BLOCK*
		ML	MG	
LOCAL INFILTRATION	0.25	UP TO 60	UP TO 150	-
LUMBAR EPIDURAL				
SURGICAL OPERATIONS	0.5	10 TO 20	50 TO 100	MODERATE TO COMPLETE
ANALGESIA IN LABOUR	0.5	6 TO 12	30 TO 60	MODERATE TO COMPLETE
	0.25	6 TO 12	15 TO 30	MINIMAL
CAUDAL EPIDURAL				
SURGICAL OPERATIONS	0.5	15 TO 30	75 TO 150	MODERATE TO COMPLETE
CHILDREN (AGED UP TO 10 YEARS)				
UP TO LOWER THORACIC (T10)	0.25	0.3 - 0.4 ml/kg	0.75 - 1.0 mg/kg	
UP TO MID- THORACIC (T6)	0.25	0.4 - 0.6 ml/kg	1.0 - 1.5 mg/kg	
IF TOTAL AMOUNT GREATER THAN 20 ML REDUCE CONCENTRATION TO 0.2%.				
ANALGESIA IN LABOUR	0.5	10 TO 20	50 TO 100	MODERATE TO COMPLETE
	0.25	10 TO 20	25 TO 50	MODERATE
PERIPHERAL NERVES	0.5	UP TO 30	UP TO 150	MODERATE TO COMPLETE
	0.25	UP TO 60	UP TO 150	SLIGHT TO MODERATE
SYMPATHETIC BLOCKS	0.25	20 TO 50	50 TO 125	-

*With continuous (intermittent) techniques, repeat doses increase the degree of motor block. The first repeat dose of 0.5% may produce complete motor block for intra-abdominal surgery.

4.3 CONTRAINDICATIONS

Bupivacaine hydrochloride solutions are contra-indicated in patients with a known hypersensitivity to local anaesthetic agents of the amide type or to other components of the injectable formulation.

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

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

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 drugs, 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.

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 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 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 drug. 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 treated with anti-arrhythmic drugs 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 drugs (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 drugs.

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.

Paracervical block may have a greater adverse effect on the foetus than other nerve blocks used in obstetrics. Due to the systemic toxicity of bupivacaine special care should be taken when using bupivacaine for paracervical block.

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.

Each 10 ml of Bupivacaine 0.25%w/v solution for injection contains approximately 1.47 mmol (33.8 mg) sodium. To be taken into consideration by patients on a controlled sodium diet.

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, since the systemic toxic effects are additive.

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

4.6 PREGNANCY AND LACTATION

There is no evidence of untoward effects in human pregnancy. In large doses there is evidence of decreased pup survival in rats and an embryological effect in rabbits if bupivacaine is administered in pregnancy. Bupivacaine should not therefore be given in early pregnancy unless the benefits are considered to outweigh the risks.

Foetal adverse effects due to local anaesthetics, such as foetal bradycardia, seem to be most apparent in paracervical block anaesthesia. Such effects may be due to high concentrations of anaesthetic reaching the foetus. (see 4.4)

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 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 drug should be discontinued.

4.9 OVERDOSE

Acute Systemic Toxicity

Central nervous system toxicity is a graded response with symptoms and signs of escalating severity. The first symptoms are usually light-headedness, circumoral paraesthesia, numbness of the tongue, 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 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 respiration. In severe cases apnoea may occur. Acidosis, hyperkalaemia 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 subsequent metabolism and excretion. Recovery may be rapid unless large amounts of the drug 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.

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 to 200 mg or diazepam 5 to 10 mg. Alternatively succinylcholine 50 mg – 100 mg IV may be used providing the clinician is capable of performing endotracheal intubation and managing a fully paralysed patient.

Once convulsions have been controlled and adequate ventilation of the lungs ensured, no other treatment is generally required.

Cardiac arrest due to bupivacaine can be resistant to electrical defibrillation and resuscitation must be continued energetically for a prolonged period.

High or total spinal blockade causing respiratory paralysis and hypotension during epidural anaesthesia should be treated by ensuring and maintaining a patent airway and giving oxygen by assisted or controlled ventilation.

Hypotension should be treated by the use of vasopressors, e.g. ephedrine 10-15 mg intravenously and repeated until the desired level of arterial pressure is reached. Intravenous fluids, both electrolytes and colloids, given rapidly can also reverse hypotension.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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.

5.3 PRECLINICAL SAFETY DATA

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium chloride
Sodium hydroxide
Water for injections

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 SHELF LIFE

3 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25°C.
Do not refrigerate or freeze.

6.5 NATURE AND CONTENTS OF CONTAINER

10 ml polypropylene ampoules.
Pack size: 20 ampoules x 10 ml

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

For single use only.
Use immediately after opening.
Discard any unused solution

7 MARKETING AUTHORISATION HOLDER

Taro Pharmaceuticals Ireland Ltd.,
Lourdes Road,
Roscrea,
County Tipperary,
Ireland.

8 MARKETING AUTHORISATION NUMBER(S)

PL 20910/0008

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18/04/2007

10 DATE OF REVISION OF THE TEXT

18/04/2007

BUPIVACAINE 0.5%W/V SOLUTION FOR INJECTION PL 20910/0009

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Bupivacaine 0.5% w/v solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains bupivacaine hydrochloride 5.28 mg equivalent to anhydrous bupivacaine hydrochloride 5 mg.
Each 10 ml contains bupivacaine hydrochloride 52.8 mg equivalent to anhydrous bupivacaine hydrochloride 50 mg.

The product contains sodium chloride.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection

Clear, colourless or almost colourless solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Bupivacaine Injection BP 0.25%w/v and 0.5%w/v are used for the production of local anaesthesia by percutaneous infiltration, peripheral nerve block(s) and central neural block (caudal or epidural), that is, for specialist use in situations where prolonged anaesthesia is required. Because sensory nerve block is more marked than motor block, bupivacaine is especially useful in the relief of pain, e.g. during labour.

A list of indications and the suggested dose and strength of solution appropriate for each are shown in the table below.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

The utmost care should be taken to prevent an accidental intravascular injection, always including careful aspiration. For epidural anaesthesia, a test dose of 3-5 ml of bupivacaine containing adrenaline should be administered, since an intravascular injection of adrenaline will be quickly recognised by an increase in heart rate. Verbal contact and repeated measurement of heart rate should be maintained throughout a period of 5 minutes following the test dose. Aspiration should be repeated prior to administration of the total dose. The main dose should be injected slowly, 25-50 mg/min, in incremental doses under constant contact with the patient. If mild toxic symptoms occur, the injection should be stopped immediately.

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 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. Doses

of up to 50 mg 2-hourly may subsequently be used. A total dose of up to 500 mg bupivacaine over 24 hours, which does not include the initial bolus dose, has been used routinely for many years without reports of toxicity. The dosages in the following table are recommended as a guide for use in the average adult. For young, elderly or debilitated patients, these doses should be reduced.

TYPE OF BLOCK	% CONC.	EACH DOSE		MOTOR BLOCK*
		ML	MG	
LOCAL INFILTRATION	0.25	UP TO 60	UP TO 150	-
LUMBAR EPIDURAL				
SURGICAL OPERATIONS	0.5	10 TO 20	50 TO 100	MODERATE TO COMPLETE
ANALGESIA IN LABOUR	0.5	6 TO 12	30 TO 60	MODERATE TO COMPLETE
	0.25	6 TO 12	15 TO 30	MINIMAL
CAUDAL EPIDURAL				
SURGICAL OPERATIONS	0.5	15 TO 30	75 TO 150	MODERATE TO COMPLETE
CHILDREN (AGED UP TO 10 YEARS)				
UP TO LOWER THORACIC (T10)	0.25	0.3 - 0.4 ml/kg	0.75 - 1.0 mg/kg	
UP TO MID- THORACIC (T6)	0.25	0.4 - 0.6 ml/kg	1.0 - 1.5 mg/kg	
IF TOTAL AMOUNT GREATER THAN 20 ML REDUCE CONCENTRATION TO 0.2%.				
ANALGESIA IN LABOUR	0.5	10 TO 20	50 TO 100	MODERATE TO COMPLETE
	0.25	10 TO 20	25 TO 50	MODERATE
PERIPHERAL NERVES	0.5	UP TO 30	UP TO 150	MODERATE TO COMPLETE
	0.25	UP TO 60	UP TO 150	SLIGHT TO MODERATE
SYMPATHETIC BLOCKS	0.25	20 TO 50	50 TO 125	-

*With continuous (intermittent) techniques, repeat doses increase the degree of motor block. The first repeat dose of 0.5% may produce complete motor block for intra-abdominal surgery.

4.3 CONTRAINDICATIONS

Bupivacaine hydrochloride solutions are contra-indicated in patients with a known hypersensitivity to local anaesthetic agents of the amide type or to other components of the injectable formulation.

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

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

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 drugs, 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.

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 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 4.2).

Overdosage of 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 drug. 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 treated with anti-arrhythmic drugs 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 drugs (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 drugs.

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.

Paracervical block may have a greater adverse effect on the foetus than other nerve blocks used in obstetrics. Due to the systemic toxicity of bupivacaine special care should be taken when using bupivacaine for paracervical block.

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.

Each 10 ml of Bupivacaine 0.5%w/v solution for injection contains approximately 1.40 mmol (32.3 mg) sodium. To be taken into consideration by patients on a controlled sodium diet.

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, since the systemic toxic effects are additive.

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

4.6 PREGNANCY AND LACTATION

There is no evidence of untoward effects in human pregnancy. In large doses there is evidence of decreased pup survival in rats and an embryological effect in rabbits if bupivacaine is administered in pregnancy. Bupivacaine should not therefore be given in early pregnancy unless the benefits are considered to outweigh the risks.

Foetal adverse effects due to local anaesthetics, such as foetal bradycardia, seem to be most apparent in paracervical block anaesthesia. Such effects may be due to high concentrations of anaesthetic reaching the foetus. (see 4.4)

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 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 drug should be discontinued.

4.9 OVERDOSE

Acute Systemic Toxicity

Central nervous system toxicity is a graded response with symptoms and signs of escalating severity. The first symptoms are usually light-headedness, circumoral paraesthesia, numbness of the tongue, 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 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 respiration. In severe cases apnoea may occur. Acidosis, hyperkalaemia 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 subsequent metabolism and excretion. Recovery may be rapid unless large amounts of the drug 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.

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 to 200 mg or diazepam 5 to 10 mg. Alternatively succinylcholine 50 mg – 100 mg IV may be used providing the clinician is capable of performing endotracheal intubation and managing a fully paralysed patient.

Once convulsions have been controlled and adequate ventilation of the lungs ensured, no other treatment is generally required.

Cardiac arrest due to bupivacaine can be resistant to electrical defibrillation and resuscitation must be continued energetically for a prolonged period.

High or total spinal blockade causing respiratory paralysis and hypotension during epidural anaesthesia should be treated by ensuring and maintaining a patent airway and giving oxygen by assisted or controlled ventilation.

Hypotension should be treated by the use of vasopressors, e.g. ephedrine 10-15 mg intravenously and repeated until the desired level of arterial pressure is reached. Intravenous fluids, both electrolytes and colloids, given rapidly can also reverse hypotension.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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.

5.3 PRECLINICAL SAFETY DATA

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium chloride
Sodium hydroxide
Water for injections

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 SHELF LIFE

3 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25°C.
Do not refrigerate or freeze.

6.5 NATURE AND CONTENTS OF CONTAINER

10 ml polypropylene ampoules.

Pack size: 20 x 10 ml ampoules

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

For single use only.
Use immediately after opening.
Discard any unused solution

7 MARKETING AUTHORISATION HOLDER

Taro Pharmaceuticals Ireland Ltd.,
Lourdes Road,
Roscrea,
County Tipperary,
Ireland.

8 MARKETING AUTHORISATION NUMBER(S)

PL 20910/0009

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18/04/2007

10 DATE OF REVISION OF THE TEXT

18/04/2007

PATIENT INFORMATIOIN LEAFLET
BUPIVACAINE 0.25%W/V SOLUTION FOR INJECTION
PL 20910/0008

BUPIVACAINE 0.5%W/V SOLUTION FOR INJECTION
PL 20910/0009

PACKAGE LEAFLET: INFORMATION FOR THE USER

Bupivacaine 0.25% w/v, 0.5% w/v solution for injection

Bupivacaine Hydrochloride

Read all of this leaflet carefully before you start using this medicine.
Keep this leaflet. You may need to read it again.
If you have further questions, please ask your doctor or pharmacist.
This medicine has been prescribed for you. Do not pass it on to others. It may harm them even if their symptoms are the same as yours.
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT BUPIVACAINE SOLUTION FOR INJECTION IS AND WHAT IT IS USED FOR

Bupivacaine hydrochloride is a local anaesthetic. It belongs to a group of medicines called amide-type local anaesthetics. It produces a loss of feeling or sensation that is confined to one part of the body.

Bupivacaine solution for injection is used for
- surgical operations, including obstetric operations such as caesarean section
- relief of acute pain including labour pain or pain after an operation
- diagnosis and treatment of chronic pain.

2. BEFORE YOU USE BUPIVACAINE SOLUTION FOR INJECTION

Do not use Bupivacaine solution for injection

- If you are hypersensitive (allergic) to bupivacaine or local anaesthetics of the amide type or to any of the other ingredients in this medicine. An allergic reaction may be recognized as a rash, itching, swollen face or lips, or shortness of breath.
- To produce local anaesthesia by injecting it into a vein of a limb that has been isolated from the circulation by means of a tourniquet (a technique called intravenous regional anaesthesia or Bier's-block).

Epidural anaesthesia should not be used if you are suffering from:
- diseases of the central nervous system such as meningitis, polio
- problems with your spinal cord due to anaemia
- severe headache
- tumours in your brain or spinal cord
- tuberculosis of the spine
- an infection of the skin at or near the site of injection
- very low blood pressure or low blood volume
- problems with clotting of your blood.

Take special care with Bupivacaine solution for injection

- if you suffer from any liver disorder
- if you suffer from a blood infection (septicaemia)
- if you suffer from very low or very high blood pressure
- if you suffer from dehydration or any recent vomiting, diarrhoea or blood loss
- if you suffer from heart disease
- if you suffer from a tumour or an accumulation of fluid in the abdomen.

You should talk to your doctor if you think this could apply to you.

Taking other medicines

Please inform your doctor if you are taking any medicines, even those not prescribed. Taking some medicines together can be harmful. Remember that the doctor at the hospital may not have been informed if you have recently begun a course of treatment for another illness. In particular tell your doctor if you are taking
- other local anaesthetics (such as lidocaine)
- volatile anaesthetics e.g. chloroform, halothane, cyclopropane, trichlorethylene, or other related agents
- anticoagulants (to prevent blood clotting)
- drugs to control your heart beat (including tocainide)
- betablockers which are used to control your heart beat or to lower your blood pressure.

Pregnancy and breastfeeding

If you are pregnant or you think you may be pregnant, you should inform your doctor who will decide whether or not you should be given bupivacaine. Ask your doctor or pharmacist for advice before taking any medicine.

Bupivacaine may get into breast milk. If you are breast-feeding you should discuss options with your doctor. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Do not drive or use any tools or machines because bupivacaine may interfere with your ability to do so safely. Ask your doctor when it would be safe to resume these activities.

Important information about some of the ingredients of Bupivacaine solution for injection

Each 10 ml of Bupivacaine 0.25%w/v solution for injection contains 1.47 mmol (33.8 mg) of sodium. Each 10 ml of Bupivacaine 0.5%w/v solution for injection contains 1.40 mmol (32.3 mg) sodium. To be taken into consideration by patients on a controlled sodium diet.

3. HOW TO USE BUPIVACAINE SOLUTION FOR INJECTION

Bupivacaine solution for injection will be given to you by your doctor who will have the necessary

knowledge and experience in the technique of epidural anaesthesia.

Your doctor will decide what dose is right for you. This will normally be between 15 – 150 mg of bupivacaine hydrochloride. The dose will depend on your size, your state of health, the part of the body that the medicine is injected into and what the medicine is being used for. Smaller doses are used for elderly people, young children and people who are unwell.

You may be given this medicine before minor or major surgery, or during childbirth. For minor surgery, the injection will usually be given near the part of the body to be operated on. The medicine will prevent pain and cause numbness which will gradually wear off once the procedure is over. For major surgery or childbirth, you may be given an injection in your back which will take a few minutes. This will prevent pain and cause numbness in the lower half of your body which usually lasts for 3 to 4 hours.

For most procedures, one dose is enough but more doses may be needed if the procedure takes a long time.

If you use more Bupivacaine solution for injection than you should

If you think you have been given too much of this medicine tell your doctor.

If you miss a dose of Bupivacaine solution for injection

If you think you have missed a dose of this medicine, tell your doctor.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Bupivacaine solution for injection can cause side effects, although not everyone gets them.
Bupivacaine is generally well tolerated. Serious side effects are rare and usually only occur with high blood levels of bupivacaine. Tell your doctor immediately if you notice any of the following

- any signs of an allergic reaction such as a skin rash, wheeziness, swelling of the tongue or lips, or feeling suddenly weak and unwell (allergic reactions to bupivacaine are rare)
- numbness of the tongue, feeling dizzy and light-headed, blurred vision, muscle twitching, drowsiness and occasionally loss of consciousness, fits, low blood pressure and slowed breathing or heart beat which may be life threatening (these symptoms are suggestive of too much bupivacaine entering the blood stream)
- yellowing of the skin or the white of the eyes (signs of disturbed liver function, which are reversible, have been observed after repeated administration of bupivacaine).

Nerve damage can rarely occur with some types of nerve block and may result in localised areas of anaesthesia or paraesthesia (tingling or other odd sensations), loss of bladder control or loss of power in the legs. These effects may be permanent.

If any of the side effects gets serious or if you notice any side effects not mentioned in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE BUPIVACAINE SOLUTION FOR INJECTION

Keep out of the reach and sight of children.
Do not use after the expiry date, which is stated on the ampoule and carton. The expiry date refers to the last day of that month.
Do not store above 25°C.
Do not refrigerate or freeze.
Bupivacaine Injection is for single use only and should be used immediately after opening. Discard any unused solution.
Do not use the ampoule if the contents are discoloured in any way or if particles are present.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Bupivacaine solution for injection contains

The active substance is bupivacaine hydrochloride.
The other ingredients are water for injections, sodium chloride and sodium hydroxide.

What Bupivacaine solution for injection looks like and contents of the pack

Bupivacaine solution for injection is a clear, colourless, sterile solution for injection. It is available in two strengths, 0.25% w/v and 0.5% w/v. Both product strengths are available in 10 ml polypropylene ampoules packed in cartons of 20 ampoules.

Bupivacaine 0.25% w/v solution for injection: Each 1 ml of solution contains 2.5 mg of anhydrous bupivacaine hydrochloride.

Bupivacaine 0.5% w/v solution for injection: Each 1 ml of solution contains 5.0 mg of anhydrous bupivacaine hydrochloride.

Marketing Authorisation Holder and Manufacturer

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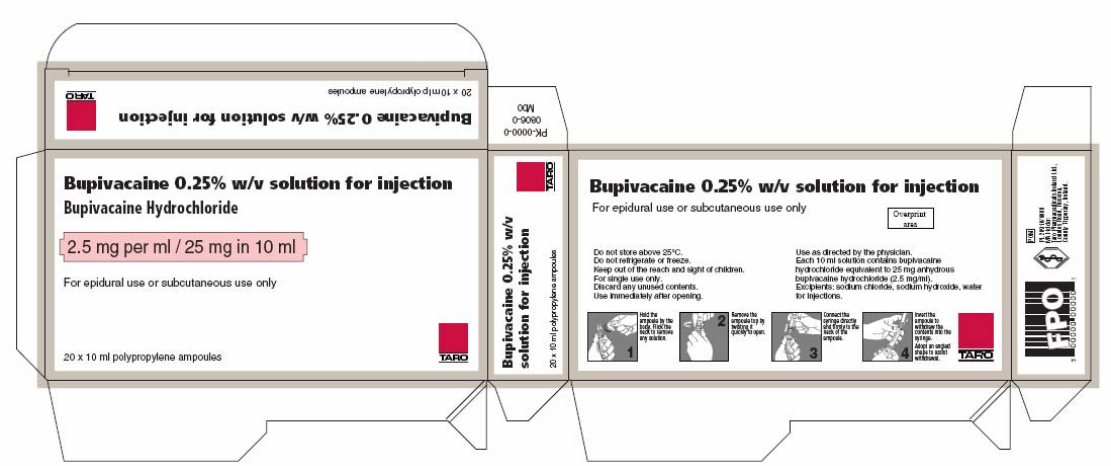
For any further information about this medicinal product, please contact the Marketing Authorisation Holder

This leaflet was last approved in 04/2007

TARO

LABELLING

BUPIVACAINE 0.25%W/V SOLUTION FOR INJECTION
PL 20910/0008



BUPIVACAINE 0.5%W/V SOLUTION FOR INJECTION
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