PIVAKAN 0.5%w/v (PLAIN) INJECTION

DESCRIPTION:
PIVAKAN 0.5%W/V (PLAIN) INJECTION (20ML VIAL): A clear, colourless sterile isotonic solution.

COMPOSITION:
PIVAKAN 0.5%W/V (PLAIN) INJECTION (20ML VIAL): Each ml contains Bupivacaine HCl Monohydrate equivalent to Bupivacaine HCl 5mg/ml.

PHARMACODYNAMICS:
Bupivacaine is a local anaesthetic of the amide type, chemically related to mepivacaine. Bupivacaine, like other local anaesthetics, causes a reversible blockade of impulse propagation along nerve fibres by preventing the inward movement of sodium ions through the nerve membrane. Local anaesthetics of the amide type are thought to act within the sodium channels of the nerve membrane.
Given as a spinal anaesthetic, bupivacaine has a rapid onset and a medium to long duration. The duration is dose-dependent. It is approximately four times more potent and toxic than lignocaine.
Bupivacaine has a rapid onset and long duration of action. The duration of analgesia from the isobaric solution is 3-4 hours in the lower thoracic and lumbar segments, and that from the hyperbaric solution is between 2-3 hours in the T_{10} - T_{12} segments.
PIVAKAN 0.5% PLAIN produces muscle relaxation in the lower limbs which lasts 3-4 hours, somewhat shorter than the duration of sensory blockade.
PIVAKAN 0.5% PLAIN is slightly hyperbaric (compared to cerebrospinal fluid) at 20°C and slightly hypobaric at 37°C. Practically it may be considered isobaric as its spread is only marginally affected by gravity. PIVAKAN 0.5% PLAIN will produce a lower level of block, for a longer duration, than the hyperbaric solution.

PHARMACOKINETICS:
Bupivacaine has a pKa of 8.1 and is extensively bound to plasma proteins (95%). Bupivacaine exhibits a high degree of lipid solubility with an oil/water partition coefficient of 27.5. These factors contribute to its prolonged duration of action.
The rate of hydrolysis in spinal fluid is slow. The majority of a dose is removed from the subarachnoid space by the venous drainage system and a smaller amount through the lymphatic system.
The maximum plasma concentration is approximately 0.4 mg/L for every 100 mg injected, this is due to slow absorption from the subarachnoid space and the small dose required for spinal anaesthesia. This means that even the maximum recommended dose (20 mg) would result in plasma levels of less than 0.1 mg/L.
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. Clearance of bupivacaine is almost entirely due to liver metabolism, and depends upon both liver blood flow and enzyme activity. The major pathway is thought to be N-dealkylation to 2,6-pipecoloxylidide (PPX). Only 6% of bupivacaine is excreted unchanged in the urine, the main metabolites being PPX and its derivatives.
Unbound bupivacaine readily crosses the placenta in equilibrium with the mother. Only about 5% of bupivacaine is unbound and available for transfer and foetal protein binding is low compared to the mother so that the total plasma concentration (free plus bound) will be lower in the foetus than in the mother.

INDICATION:
It 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: Continuous epidural infusion or intermittent bolus epidural administration for analgesia in postoperative pain or labour pain, Field block (minor nerve block and infiltration).

RECOMMENDED DOSAGE:
The following dosage recommendations should be regarded as a guide for use in the average adult. The patient's physical status and concomitant medication should be considered when deciding the dose, and the lowest dose required for adequate anaesthesia should be used. Duration varies with dose, while segmental spread may be difficult to predict, especially with the isobaric (plain) solution. The dose should be reduced in the elderly and in patients in the late stages of pregnancy.
Spinal anaesthesia for surgery:
The spread of anaesthesia obtained with both PIVAKAN 0.5% PLAIN is dependent on several factors, the most important being volume of solution injected, position of patient and rate of injection.
2-4 mL PIVAKAN 0.5% PLAIN (10-20 mg bupivacaine hydrochloride). The difference in spread between 3 and 4 mL is approximately 2 segments. The larger volume gives ½ to 1 hour longer duration of anaesthesia in the lumbar segments and more lasting motor blockade. When injected into the L_3 - L_4 interspace with the patient in the supine horizontal position, 3 mL of PIVAKAN 0.5% PLAIN spreads to T_5 - T_7. If the patient is placed in the sitting position the anaesthesia spreads to T_4 - T_5.
Note: Spinal injections should only be made after the subarachnoid space has been clearly identified by lumbar puncture. No drug should be injected until clear cerebrospinal fluid (CSF) is seen to escape from the spinal needle or it is detected by aspiration.
Hypotension:
During spinal anaesthesia, a marked fall in blood pressure and/or intercostal paralysis may be seen, possibly due to the use of excessive doses or improper positioning of the patient. Hypotension and bradycardia may occur as a result of sympathetic blockade. Standard textbooks should be consulted with respect to techniques for administration of PIVAKAN for spinal anaesthesia.
Paediatrics:
PIVAKAN 0.5% PLAIN and may be used in children. One of the differences between small children and adults is a relatively high CSF volume in infants and neonates, requiring a relatively larger dose/kg to produce the same level of block as compared to adults.

Body Weight (kg)	Dose (mg/kg)
<5	0.40-0.50 mg/kg
5 to 15	0.30-0.40 mg/kg
15 to 40	0.25-0.30 mg/kg

Postoperative Analgesia:
Intermittent epidural: Infuse 4–8 mL of PIVAKAN 0.5% PLAIN at rate of 1–2 mL/hr.
Continuous epidural: Dilute PIVAKAN 0.5% PLAIN to 0.125% and Infuse at rate of 15 mL/hr.
Analgesia in Labour:
6 to 12 ml (30 to 60mg of Bupivacaine) for moderate to complete motor block. 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. 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 150mg bupivacaine hydrochloride. Doses of up to 50mg 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 dosage as abovementioned is recommended as a guide for use in the average adult. For young, elderly or debilitated patients, these doses should be reduced.

ROUTE OF ADMINISTRATION: Infiltration or epidural injection

CONTRAINDICATIONS:
General contraindications related to intrathecal anaesthesia should be taken into account:
Absolute: Allergy or hypersensitivity to amide type local anaesthetics. Detection of suspected sensitivity by skin testing is of limited value.
Acute active diseases of the cerebrospinal system such as meningitis, tumours (primary or secondary), poliomyelitis, subacute combined degeneration of the spinal cord, cranial haemorrhage, demyelinating disease and raised intracranial pressure.
Spinal stenosis and active disease (eg. spondylitis, tumour) or recent trauma (eg. fracture) in the vertebral column.
Local anaesthetic techniques must not be used when there is inflammation and/or sepsis in the region of the proposed injection or in the presence of septicaemia.
Uncorrected hypotension, cardiogenic or hypovolaemic shock.
Coagulation disorders or ongoing anti-coagulation treatment.
Pernicious anaemia with subacute combined degeneration of the spinal cord.
Relative: Arthritis and other diseases of the vertebral column are relative contraindications due to technical difficulties in performing a spinal injection.

WARNINGS & PRECAUTIONS:
When any local anaesthetic agent is used, resuscitative equipment and agents, including oxygen, should be immediately available in order to manage possible adverse reactions involving the cardiovascular, respiratory or central nervous systems.
The safety and effectiveness of PIVAKAN depend on proper dosage, correct technique and adequate precautions. Standard textbooks should be consulted for specific techniques and precautions for spinal anaesthetic procedures. If signs of acute systemic toxicity or total spinal block appear, injection of the local anaesthetic should be stopped immediately.

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Patients in poor general condition due to ageing or other compromising factors such as partial or complete heart conduction block, advanced liver or renal dysfunction require special attention although regional anaesthesia may be the optimal choice for surgery in these patients.
The possibility of hypotension and bradycardia following epidural or subarachnoid blockade should be anticipated and appropriate precautions taken, including the prior establishment of an intravenous line and the availability of vasopressor agents and oxygen.
Hypotension is common in patients with hypovolaemia due to haemorrhage or dehydration and in those with aortocaval occlusion due to abdominal tumours or the pregnant uterus in late pregnancy. Hypotension is poorly tolerated by patients with coronary or cerebrovascular disease.
Bupivacaine should be used with caution in patients with known medicine sensitivities.
Bupivacaine should be used with caution in patients with genetic predisposition to malignant hyperthermia as the safety of amide local anaesthetic agents in these patients has not been fully established. A standard protocol for the management of malignant hyperthermia should be available.
Spinal anaesthesia can be unpredictable and very high blocks are sometimes encountered with paralysis of the intercostal muscles, and even the diaphragm, especially in pregnancy. On rare occasions it will be necessary to assist or control ventilation.
Chronic neurological disorders, such as multiple sclerosis, hemiplegia due to stroke etc. are not thought to be adversely affected by spinal anaesthesia, but call for caution.
There is an increased risk for high or total spinal blockade in the elderly and in patients in the late stages of pregnancy. The dose should therefore be reduced in these patients (see DOSAGE AND ADMINISTRATION).
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 coordination even in the absence of overt CNS toxicity and may temporarily impair locomotion and alertness.

INTERACTION WITH OTHER MEDICAMENTS:

Anti-arrhythmic agents: Bupivacaine should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics, eg tocainide, since the systemic toxic effects are additive.

USE IN PREGNANCY & LACTATION:

Use in Pregnancy: It is reasonable to assume that a large number of pregnant women and women of child-bearing age have been given bupivacaine. No specific disturbances to the reproductive process have so far been reported, e.g. no increased incidence of malformations.
It should be noted that the dose should be reduced in patients in the late stages of pregnancy (see DOSAGE AND ADMINISTRATION).
Local anaesthetics cross the placental barrier rapidly. A lower foetal/maternal ratio (0.2 - 0.4) than for other local anaesthetics has been observed for bupivacaine.

Use in Lactation: With recommended doses, bupivacaine enters breast milk in such small quantities that there is generally no risk of affecting the breast-fed child.
At maternal serum levels of up to 0.45 µg/mL produced by the epidural use of bupivacaine for vaginal delivery, bupivacaine could not be detected in breast milk during the first 24 hours after delivery (detection limit 0.02 µg/mL).

SIDE EFFECTS:

In general, almost all the side effects seen with spinal anaesthesia are due to the nerve blockade itself and not to the agent used. These effects include hypotension, bradycardia and post dural puncture headache.
High or Total Spinal Blockade: Severe adverse reactions following spinal bupivacaine are rare but may occur in connection with extensive (total) spinal blockade. Total spinal blockade will result in cardiovascular and respiratory depression. The cardiovascular depression is caused by an extensive sympathetic blockade which may result in profound hypotension and bradycardia, or even cardiac arrest. Ventilatory depression is caused by blockade of respiratory muscles including the diaphragm.
Acute systemic toxicity: In view of the low dosage employed, systemic adverse reactions are rarely associated with spinal anaesthesia. Systemic adverse reactions are characterised by numbness of the tongue, light-headedness, dizziness and tremor followed by convulsions and cardiovascular reactions. The cardiovascular reactions are depressant and may be characterised by hypotension, myocardial depression, bradycardia and possibly cardiac arrest.
Allergy: Allergy to amide type local anaesthetics is very rare but may be present as allergic dermatitis, bronchospasm or anaphylaxis.
Neurological reactions: Neurological damage is a rare, though recognised, consequence of spinal anaesthesia. It may have one of several causes such as direct injury to the spinal cord or spinal nerves, anterior spinal artery syndrome, injection of an irritant substance, injection of a non-sterile solution or the development of a space occupying lesion (haematoma or abscess) within the spinal canal. These may result in localised areas of paraesthesia or anaesthesia, motor weakness, loss of sphincter control and paraplegia. Occasionally these are permanent. Neurological complications of this type have been reported with all local anaesthetics used for spinal anaesthesia.

SYMPTOMS AND TREATMENT OF OVERDOSE:

PIVAKAN 0.5% PLAIN used as recommended are not likely to cause blood levels high enough to cause systemic toxicity. However, if other local anaesthetics are concomitantly administered, toxic effects are additive and may cause systemic toxic reactions.
Systemic toxicity to amide type local anaesthetics is initially manifested as CNS excitation e.g. yawning, restlessness, excitement, nervousness, blurred vision, nausea and vomiting, muscle twitching and in more severe cases, convulsions. Excitation may be followed by CNS depression with drowsiness, respiratory failure, coma, cardiac arrhythmias and cardiac arrest.
Treatment of overdosage: Treatment of a patient with toxic manifestations consists of ensuring adequate ventilation and arresting convulsions. Assisted or controlled ventilation should be maintained with oxygen, if required.
If convulsions occur, intravenous diazepam should be administered incrementally. Sodium thiopentone (5 mg/kg) may be used if diazepam is unavailable or ineffective. If convulsions interfere with breathing and/or are not rapidly controlled by specific anticonvulsant medication, suxamethonium (1-2 mg/kg) may be used to paralyse the patient. Artificial ventilation must then be instituted.
If ventricular fibrillation or cardiac arrest occurs, effective cardiovascular resuscitation treatment must be instituted and maintained for a prolonged period if necessary.

INCOMPATIBILITIES:

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

STORAGE CONDITIONS:

Store below 30˚C. Protect from light. Keep out of reach of children. JAUHKAN DARIPADA KANAK-KANAK.
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 PIVAKAN and metal surfaces such as metal bowls, cannulae and syringes with metal parts.
Use once only and discard any remaining portion. The solution should be used immediately after opening the vials. Solutions showing discolouration should not be used.

SHELF LIFE:

Please refer to outer package.

PACK SIZE:

Pack in 25 vials x 20 ml.

PRODUCT REGISTRATION HOLDER & MANUFACTURER:

DUOPHARMA (M) SDN BHD
Lot 2599 Jalan Seruling 59, Kawasan 3,
Taman Klang Jaya, 41200 Klang,
Selangor Darul Ehsan,
MALAYSIA

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