REGIVELL® SPINAL 0.5% HEAVY

COMPOSITION
Each mL of solution for injection contains:
- Bupivacaine Hydrochloride Monohydrate equivalent to
  Bupivacaine Hydrochloride 5 mg
- Glucose Monohydrate 80 mg

PHARMACEUTICAL FORM
Solution for Injection
Clear and colourless solution, practically free from visible particles

PHARMACOLOGICAL PROPERTIES
Pharmacotherapeutic group (ATC code): N01B B01
Bupivacaine, like other local anaesthetics, causes a reversible blockade of impulse propagation along nerve fibres by preventing the inward movement of sodium ions through the nerve membrane. Local anaesthetics of the amide type are thought to act within the sodium channels of the nerve membrane.
Local anaesthetic drugs may have similar effects on excitable membranes in the brain and myocardium. If excessive amounts of drug reach the systemic circulation rapidly, symptoms and signs of toxicity will appear, emanating mainly from the central nervous system and cardiovascular systems.
Central nervous system toxicity usually precedes the cardiovascular effects as it occurs at lower plasma concentrations. Direct effects of local anaesthetics on the heart include slow conduction, negative inotropism and eventually cardiac arrest.
Indirect cardiovascular effects, e.g. hypotension and bradycardia, may occur after epidural or spinal administration depending on the extent of the concomitant sympathetic block.

Pharmacokinetics
Bupivacaine is a long-acting, amide-type local anaesthetic chemically related to lignocaine and mepivacaine. It is approximately four times as potent as lignocaine. The onset of the blockade is slower than with lignocaine, especially when anaesthetising large nerves.
Bupivacaine has a total plasma clearance of 0.58 L/min, a volume of distribution at steady-state of 73 L, an elimination half-life of 2.7 hours and an intermediate hepatic extraction ratio of 0.40 following experimental IV administration in adults. The terminal elimination half-life is prolonged
in the newborn to approximately 8 hours. In children aged over 3 months the elimination half-life is similar to that in adults. Bupivacaine is mainly bound to a1-acid glycoprotein in plasma with a plasma binding of 96%.
Regivell have a rapid onset and long duration of action. The duration of analgesia from the isobaric solution is 3 - 5 hours in the lower thoracic and lumbar segments, and that from the hyperbaric solution is between 2 - 3 hours in the T10 - T12 segments.
Regivell produces moderate muscle relaxation in the lower extremities lasting 2 - 3 hours. Motor blockade of the abdominal muscles makes the solution suitable for performance of abdominal surgery lasting 45 - 60 minutes. The duration of motor blockade does not exceed the duration of analgesia.
An increase in a1 -acid glycoprotein, which occurs postoperatively after major surgery, may cause an increase in the total plasma concentration of bupivacaine. The level of free drug will remain the same. This explains why total plasma concentrations above the apparent toxic threshold level of 2.6-3.0 mg/L are apparently well tolerated in this situation.
Following IV administration, bupivacaine is excreted in the urine principally as metabolites with about 6% as unchanged drug. Following epidural administration, the urinary recovery of unchanged bupivacaine is about 0.2%, of pipecolylxylidine (PPX) about 1% and of 4-hydroxybupivacaine about 0.1% of the administered dose. Various pharmacokinetic parameters can be significantly altered by a number of factors including the presence of hepatic and renal disease, route of administration, age of the patient and certain concomitant medication.

THERAPEUTIC INDICATIONS
Spinal anaesthesia for surgery (urological and lower limb surgery lasting 2-3 hours, abdominal surgery lasting 45-60 minutes).

POSOLOGY AND METHOD OF ADMINISTRATION
Route of administration: For Intrathecal Injection.
As with all local anaesthetics, the dosage varies and depends upon the area to be anaesthetised, the vascularity of the tissues, the number of neuronal segments to be blocked, the depth of anaesthesia and degree of muscle relaxation required, individual tolerance, the technique of anaesthesia, and the physical condition of the patient.
The lowest dosage that results in effective anaesthesia should be used. In general, surgical anaesthesia requires the use of higher concentrations and doses than those required for analgesia. The presentations of Regivell injection solutions are for use in one patient on one occasion only. Any solution remaining from an opened container should be discarded.

Spinal anaesthesia for surgery
2 - 4 mL Regivell (10 - 20 mg bupivacaine hydrochloride).
When 3 mL Regivell was injected into the L3 - L4 interspace and patients were kept in the sitting position for 2 minutes before being placed supine, blockade spread to the T7 - T10 segment. When a similar injection was made in patients in the lateral position who were then immediately placed supine, blockade spread to the T4 - T7 segment.
The effects of injections of Regivell exceeding 4 mL have not yet been studied and such volumes can therefore not be recommended.
Note:-

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 Regivell for spinal anaesthesia.

Use in Children
The use of spinal anaesthesia in children requires a thorough knowledge of the differences between adults and children to enable the administration of adequate doses of the drug. Since a relatively high CSF volume is found in infants and neonates, proportionately larger doses per kg are required to produce the same level of block. In small children the nerves are less myelinated, allowing easier diffusion of the drug and a more rapid onset of anaesthesia, hence lower concentrations are needed to block nerve conduction. The hypotension usually seen following spinal block in adults is uncommon in children below the age of 8.
The following doses of Regivell are recommended for use in children:
0.4 - 0.5 mg/kg for infants up to 5 kg
0.3 - 0.4 mg/kg for children weighing between 5 and 15 kg
0.25 - 0.3 mg/kg for children weighing more than 15 kg
The onset of anaesthesia is slower than with lignocaine and lasts for 60 - 120 minutes.

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

Use in Debilitated or Elderly Patients
The dose should be reduced in the elderly.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
1. When any local anaesthetic agent is used, resuscitative equipment and drugs, including oxygen, should be immediately available in order to manage possible adverse reactions involving the cardiovascular, respiratory or central nervous systems.
   Because of the possibility of hypotension and bradycardia following major blocks, an iv cannula should be inserted before the local anaesthetic is injected. Delay in proper management of dose-related toxicity, under-ventilation from any cause and/or altered sensitivity may lead to the development of acidosis, cardiac arrest and death.
2. Injection should always be made slowly with frequent aspirations to avoid inadvertent intravascular injection, which may produce toxic effects.
3. Careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness should be accomplished after each local anaesthetic injection. It should be kept in mind that at such times restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression or drowsiness may be early warning signs of CNS toxicity.
4. Local anaesthetics should be given with great caution (if at all) to patients with pre-existing abnormal neurological pathology, e.g. Myasthenia gravis. Use with extreme caution in spinal anaesthesia when there are serious diseases of the CNS or of the spinal cord, e.g. meningitis, spinal fluid block, cranial or spinal haemorrhage, tumours, poliomyelitis, syphilis, tuberculosis or metastatic lesions of the spinal cord.
5. Neurological disorders, such as multiple sclerosis, hemiplegia, paraplegia and neuromuscular disorders are not thought to be adversely affected by intrathecal anaesthesia, but call for caution. Before treatment is instituted, consideration should be taken if the benefits outweigh the possible risks for the patient.
6. Patients with hypovolaemia can develop sudden and severe hypotension during intrathecal anaesthesia.
7. A rare, though severe, adverse reaction following spinal anaesthesia is high or total spinal blockade resulting in cardiovascular and respiratory depression. The cardiovascular depression is caused by extensive sympathetic blockade which may result in profound hypotension and bradycardia, or even cardiac arrest. Respiratory depression may be caused by blockade of the innervation of the respiratory muscles, including the diaphragm.
8. Neurological injury is a rare consequence of intrathecal anaesthesia and may result in paraesthesia, anaesthesia, motor weakness and paralysis. Occasionally these are permanent.
9. 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.
10. The safety and effectiveness of Regivell depend on proper dosage, correct technique and adequate precautions. Standard textbooks should be consulted for specific techniques and precautions for spinal anaesthetic procedures.
11. The lowest dosage that results in effective anaesthesia should be used (see Posology and Method Administration). Repeated injections of Regivell may cause accumulation of bupivacaine or its metabolites and result in toxic effects. Tolerance to elevated blood levels varies with the status of the patient. Elderly, young or debilitated patients, including those with partial or complete conduction block, advanced liver disease or severe renal impairment, should be given reduced doses commensurate with their age and physical condition.
    Caution should be used when administering bupivacaine to children under 12 years of age.
12. Bupivacaine may cause acute toxicity affects 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. However, High systemic concentrations are not expected with doses normally used for intrathecal anaesthesia.
13. Bupivacaine should be given with great caution to patients with epilepsy, impaired cardiac conduction, bradycardia, severe shock or digitalis intoxication. Bupivacaine should also be administered with great caution to patients with impaired cardiovascular function as they may be less able to compensate for functional changes associated with the prolongation of AV conduction produced by these drugs. *Patients being treated with anti-arrhythmic drugs class III (e.g. Amiodarone) should be under close surveillance and ECG monitoring since cardiac effects may be additive.*
    In patients with stokes-adams syndrome or wolff-parkinson-white syndrome extreme care should be taken to avoid accidental arterio-venous injection.
14. Bupivacaine is eliminated primarily by hepatic metabolism and changes in hepatic function may have significant consequences. Bupivacaine has an intermediate clearance which depends on its unbound fraction and intrinsic metabolic clearance. Bupivacaine should therefore be used with caution in patients with severe hepatic disease.
15. Bupivacaine should be used with caution in patients with severe renal dysfunction because acidosis and reduced plasma protein concentration, which are frequently seen in these patients, may increase the risk of systemic toxicity. Patients with hyperthyroidism are also more susceptible to toxicity with bupivacaine.

16. Bupivacaine should be used with caution in patients with known drug sensitivities.
17. 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.
18. Intrathecal anaesthesia may lead to hypotension and bradycardia. The risk of such effects can be reduced, e.g., by injecting a vasopressor. Hypotension should be treated promptly with a sympathomimetic intravenously, repeated as necessary.

SIDE EFFECTS
Adverse reactions to bupivacaine are similar in nature to those observed with other amide local anaesthetics. These adverse reactions are, in general, dose-related and may result from high plasma levels caused by excessive dosage or rapid absorption, or may result from a hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient.
A rare, though severe, adverse reaction following spinal bupivacaine is 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.

In view of the low dosage employed, systemic adverse reactions are rarely associated with spinal anaesthesia. The following types are those most commonly reported:
Central Nervous System
CNS manifestations are excitatory and/or depressant and may be characterised by lightheadedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred vision, nausea, vomiting, sensations of heat, cold or numbness, *urinary retention, paraesthesia, dysaesthesia,* twitching, tremors, convulsions, unconsciousness, respiratory depression and/or arrest, agitation, difficulty swallowing and slurred speech.
The excitatory manifestations may be very brief or may not occur at all, in which case the first manifestation of toxicity may be drowsiness merging into unconsciousness and respiratory arrest.
Drowsiness following administration of bupivacaine is usually an early sign of a high blood level of the drug and may occur as a result of rapid absorption. In unconscious patients, circulatory collapse should be watched as CNS effects may not be apparent as an early manifestation of toxicity may in some cases progress to frank convulsions and ultimately lead to respiratory depression and/or arrest. It is crucial to have resuscitative equipment and anticonvulsant drugs available to manage such patients. (see Overdose -Treatment of Overdosage).

Cardiovascular
Cardiovascular manifestations are usually depressant and are characterised by bradycardia, hypotension, and cardiovascular collapse, which may lead to cardiac arrest.
Musculoskeletal, connective tissue and bone disorders
Muscle weakness, back pain.

Haemodynamic
Regional anaesthesia may lead to maternal hypotension.

Allergic
Allergic reactions are characterised by cutaneous lesions, urticaria, oedema or anaphylactoid reactions.
Allergy to amide type local anaesthetics is rare. If such a reaction occurs, it should be managed by conventional means.
The detection of sensitivity by skin testing is of doubtful value.

Neurologic
The incidences of adverse reactions associated with the use of local anaesthetics may be related to the total dose of local anaesthetic administered and are also dependent on the particular drug used, the route of administration and the physical status of the patient.
Adverse effects experienced subsequent to spinal administration of local anaesthetic may include spinal block of varying magnitude (including total spinal block), hypotension secondary to spinal block, loss of bladder and bowel control and loss of perineal sensation and sexual function.
Persistent motor, sensory and/or autonomic (sphincter control) deficit of some lower spinal segments with slow recovery (several months) or incomplete recovery have been reported in rare instances. Backache and headache have also been noted following use of this anaesthetic procedure.
Paresis, paraplegia, paralysis, neuropathy and arachnoiditis have been observed.
The effects of systemic overdose and unintentional intravascular injection may involve the central nervous system and/or the cardiovascular system (see Overdose). Inadvertent subarachnoid injection of high doses of local anaesthetic may lead to CNS depression, respiratory arrest and cardiovascular collapse.

CONTRAINDICATIONS
1. Allergy or hypersensitivity to amide type local anaesthetics
   Detection of suspected sensitivity by skin testing is of limited value.
2. Intravenous administration.
3. 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.
4. Certain conditions of the bones of the vertebral column such as tuberculosis, tumours and osteomyelitis.
5. Arthritis, spondylitis, spinal stenosis and other diseases of the vertebral column, or recent trauma due to fracture, rendering spinal puncture impossible.
6. Local anaesthetics are contraindicated for epidural and spinal anaesthesia in patients with uncorrected hypotension or coagulation disorders or in patients receiving anti-coagulant treatment.
7. 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.
8. Pernicious anaemia with subacute combined degeneration of the spinal cord.
9. Cardiogenic or hypovolaemic shock

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, since the systemic toxic effects are additive.

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

PREGNANCY AND LACTATION
Use during pregnancy
Category A
The safe use of bupivacaine during pregnancy has not been established. Although bupivacaine has been used extensively for surgical procedures during pregnancy with no reports of ill effects to mother or fetus, there are no adequate and well-controlled studies in pregnant women of the effect of bupivacaine on the developing fetus. It should therefore be used cautiously during pregnancy, other than labour, with the dose being reduced in patients in the late stages of pregnancy. Bupivacaine has been effectively used for obstetrical analgesia and adverse effects on the course of labour or delivery are rare. After epidural administration of bupivacaine to women in labour, bupivacaine crosses the placental barrier. However, concentrations in umbilical veins are lower than those found in the maternal circulation. It has been suggested that blood glucose levels should be checked in newborns after obstetric regional anaesthesia.

Use during lactation
Bupivacaine passes into breast milk. The amount of bupivacaine appearing in breast milk from a nursing mother receiving parenteral bupivacaine is unlikely to lead to a significant accumulation of the parent drug in the breast-fed infant.
At maternal serum levels of up to 0.45 microgram/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 microgram/mL).
The remote possibility of an idiosyncratic or allergic reaction in the breast-fed infant from bupivacaine remains to be determined.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Spinal anaesthesia has little effect on mental function and coordination but will temporarily impair locomotion and alertness.

LIST OF EXCIPIENTS
Glucose monohydrate, sodium hydroxide, water for injection and nitrogen (low oxygen.

SPECIAL PRECAUTIONS FOR STORAGE
Store below 30°C. Do not freeze.

SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING
As the solution is free from preservatives, they should be use immediately after opening of the container. Any remaining solution should be discarded.
Since Regivell contains glucose, caramelization may occur during autoclaving. This preparation should be therefore not be re-sterilized.

PRESENTATION
Box, 5 ampoules @ 4 mL

PRESCRIPTION ONLY MEDICINE

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Manufactured by :
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Pack. Code