REGIVELL® HEAVY 0.5% Solution for Injection

Bupivacaine Hydrochloride Solution for Injection

COMPOSITION
Each mL of solution for injection contains Bupivacaine hydrochloride 5 mg.

Excipients: Glucose monohydrate, sodium hydroxide, and water for injection
Description: Clear solution, practically free from visible particles and colorless.

PHARMACODYNAMICS
Pharmacotherapeutic group (ATC code): N01B B01
Bupivacaine is a long acting local anaesthetic agent of the amide type.
Moderate muscular relaxation of lower extremities.
Motor blockade of the abdominal muscles.
Regivell Heavy is hyperbaric and its initial spread in the intrathecal space is affected by gravity.

PHARMACOKINETICS
Rapid onset of action and long duration i.e. T10–T12 segments – duration 2–3 hours. Muscular relaxation of lower extremities lasts 2–2.5 hours.
Blockade of the abdominal muscles lasts 45–60 minutes. The duration of motor blockade does not exceed duration of analgesia.
In children the pharmacokinetics are similar to that in adults.

INDICATION
Spinal anesthesia for surgery (urological and lower limb surgery lasting 2 – 3 hours, abdominal surgery lasting 45 – 60 minutes).

RECOMMENDED DOSAGE

Regivell Heavy should only be used by clinicians with experience of regional anaesthesia or under their supervision. The lowest possible dose for adequate anaesthesia should be used.
The doses given below are guides for adults and the dosage should be adjusted to the individual patient.
The dose should be reduced in the elderly and in patients in the late stages of pregnancy.

Body weight (kg)	Dose (mL)	Dose (mg)	Time to onset of effect in minutes (approx.)	Duration of effect in hours (approx.)
Urological surgery	1.5 - 3 mL	7.5 - 15 mg	5 - 8 min	2 - 3 hours
Surgery on lower limbs, including hip surgery	2 - 4 mL	10 - 20 mg	5 - 8 min	2 - 3 hours
Abdominal surgery (including caesarean section)	2 - 4 mL	10 - 20 mg	5 - 8 min	45 - 60 min

The recommended site of injection is below L3-L4 intervertebral space.

There is currently no experience of doses higher than 20 mg.

A spinal injection is given only after the subarachnoid space has been clearly identified by means of lumbar puncture (clear cerebrospinal fluid runs out via the spinal needle or is seen on aspiration). In the event of unsuccessful anaesthesia, a new attempt to administer the drug should only be made by injecting at a different level and with a smaller volume. One cause of lack of effect may be poor intrathecal distribution of the drug, and this can be helped by altering the patient's position.

ROUTE OF ADMINISTRATION
For Intratechal injection

CONTRAINDICATIONS
Hypersensitivity to the active substance or to any of the excipients.Hypersensitivity to local anaesthetics of the amide type.
Intrathecalanaesthesia, regardless of the local anaesthetic used, has its own contraindications, 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.
- Spinal stenosis and active disease (e.g. spondylitis, tuberculosis, tumour) or recent trauma (e.g. fracture) in the vertebral column.
- Septicaemia.
- Pyogenic infection of the skin at or adjacent to the site of lumbar puncture.
- Cardiogenic or hypovolaemic shock.
- Coagulation disorders or ongoing anticoagulation treatment.

WARNINGS AND PRECAUTIONS
Intrathecal anaesthesia should only be undertaken by clinicians with the necessary knowledge and experience.
Regional anaesthetic procedures should always be performed in a properly equipped and staffed area. Resuscitative equipment and drugs should be immediately available and the anaesthetist should remain in constant attendance.
Intravenous access, e.g. an i.v. infusion, should be in place before starting the intrathecalanaesthesia. The clinician responsible should take the necessary precautions to avoid intravascular injection and be appropriately trained and familiar with the diagnosis and treatment of side effects, systemic toxicity and other complications. If signs of acute systemic toxicity or total spinal block appear, injection of the local anaesthetic should be stopped immediately, see sections Side effects and Symptoms and treatment of overdose.
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 or injection into highly vascular areas.
Ventricular arrhythmia, ventricular fibrillation, sudden cardiovascular collapse and death have been reported in connection with high systemic concentrations of bupivacaine. Should cardiac arrest occur, a successful outcome may require prolonged resuscitative efforts. High systemic concentrations are not expected with doses normally used for intrathecalanaesthesia.
There is an increased risk of high or total spinal blockade, resulting in cardiovascular and respiratory depression, in the elderly and in patients in the late stages of pregnancy. The dose should therefore be reduced in these patients.
Intrathecalanaesthesia with any local anaesthetic can cause hypotension and bradycardia which should be anticipated and appropriate precautions taken. These may include preloading 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 intrathecalanaesthesia.
Intrathecalanaesthesia 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.
Neurological injury is a rare consequence of intrathecalanaesthesia and may result in paraesthesia, anaesthesia, motor weakness and paralysis. Occasionally these are permanent.
Before treatment is instituted, consideration should be taken if the benefits outweigh the possible risks for the patient.
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.
Patients treated with anti-arrhythmic drugs class III (e.g. amiodarone) should be kept under close surveillance and
ECG monitoring considered, since cardiac effects may be additive.

INTERACTIONS WITH OTHER MEDICAMENTS
Bupivacaine should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics, e.g. certain anti-arrhythmics, such as lidocaine and mexiletine, since the systemic toxic effects are additive.
Specific interaction studies with bupivacaine and anti-arrhythmic drugs class III (e.g. amiodarone) have not been performed, but caution is advised.

Incompatibilities
This medicinal product must not be mixed with other medicinal products.

FERTILITY, PREGNANCY AND LACTATION
Pregnancy
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 injection is administered in pregnancy. Bupivacaine injection should not therefore be given in early pregnancy unless the benefits are considered to outweigh the risks.
It should be noted that the dose should be reduced in patients in the late stages of pregnancy.

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

Effects on Ability to Drive and Use Machines
Regivell Heavy has minor influence on the 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 locomation and alertness.

UNDESIRABLE EFFECTS
General
Tabulated list of adverse reactions
The adverse reaction profile for Regivell Heavy is similar to those for other long acting local anaesthetics used for intrathecalanaesthesia.

System Organ Class	Frequency Classification	Adverse Drug Reaction
Immune system disorders	Rare	Allergic reactions, anaphylactic shock
Nervous system disorders	Common	Postdural puncture headache
	Uncommon	Paraesthesia, paresis, dysaesthesia
	Rare	Total unintentional spinal block, paraplegia, paralysis, neuropathy, arachnoiditis
Cardiac disorders	Very Common	Hypotension, bradycardia
	Rare	Cardiac arrest
Respiratory, thoracic and mediastinal disorders	Rare	Respiratory depression
Gastrointestinal disorders	Very Common	Nausea
	Common	Vomiting
Musculoskeletal and connective tissue disorders	Uncommon	Muscle weakness, back pain
Renal and urinary disorders	Common	Urinary retention, urinary incontinence

Adverse reactions caused by the drug per se are difficult to distinguish from the physiological effects of the nerve block (e.g. decrease in blood pressure, bradycardia, temporary urinary retention), events caused directly (e.g. spinalhaematoma) or indirectly (e.g. meningitis, epidural abcess) by needle puncture or events associated to cerebrospinal leakage (e.g. postdural puncture headache).

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

OVERDOSE AND TREATMENT
Regivell Heavy, used as recommended, is 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 is rarely associated with spinal anaesthesia but might occur after accidental intravascular injection.
Systemic adverse reactions are characterised by numbness of the tongue, light-headedness, dizziness and tremors, followed by convulsions and cardiovascular disorders.

Treatment of acute systemic toxicity
No treatment is required for milder symptoms of systemic toxicity but if convulsions occur then it is important to ensure adequate oxygenation and to arrest the convulsions if they last more than 15–30 seconds. Oxygen should be given by face mask and the respiration assisted or controlled if necessary. Convulsions can be arrested by injection of thiopental 100–150 mg intravenously or with diazepam 5–10 mg intravenously. Alternatively, succinylcholine 50–100 mg intravenously may be given but only if the clinician has the ability to perform endotracheal intubation and to manage a totally paralysed patient.
High or total spinal blockade causing respiratory paralysis 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.

STORAGE
Store at room temperature (below 30°C) and protect from light.

PACKAGING
Box, Glass ampoules : 5 x 4 mL.
The ampules are sterile and individually packed in blisters.

INSTRUCTION FOR USE
The solution should be used immediately after opening of the ampoule. Any remaining solution should be discarded. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

ON MEDICAL PRESCRIPTION ONLY

Manufactured by :

NOVELL PHARMACEUTICAL LABORATORIES

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Code of packaging