SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ampres 10 mg/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution for injection contains 10 mg of chloroprocaine hydrochloride

1 ampoule with 5 ml solution, contains 50 mg of chloroprocaine hydrochloride

Excipients with known effect:

1 ml of solution contains 2.8 mg sodium

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless solution.

The pH of the solution is comprised between 3.0 and 4.0.

The osmolality of the solution is comprised between 270 – 300 mOsm/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Spinal anaesthesia in adults where the planned surgical procedure should not exceed 40 minutes.

4.2 Posology and method of administration

The equipment, medicinal products and personnel capable of dealing with an emergency, e.g. maintaining the patency of the airways and administering oxygen, must be immediately available, since in rare cases severe reactions, sometimes with a fatal outcome, have been reported after using local anaesthetics, even in the absence of individual hypersensitivity in the patient's case history. The doctor in charge is responsible for taking the measures needed to avoid an intravascular injection and should be fully trained in emergency medicine and resuscitation to be ready to prevent and to treat the side effects and complication of the procedure.

Posology

Posology must be established on an individual basis in accordance with the characteristics of the specific case. When determining the dose, the patient's physical condition and the concomitant administration of other medicinal products should be taken into consideration.

The indications relating to recommended doses are valid in adults of average height and weight (approximately 70 kg) for obtaining an effective block with one single administration. There are wide individual variations with regard to extent and duration of action. The experience of the anaesthetist and knowledge of the patient's general condition are essential for establishing the dose.

With regard to posology the following guidelines are applied:

Posology Adults

Extension of sensory blockade required T10	*ml*	*mg*	*Average duration of action (minutes)*
	4	40	80
	5	50	100

The maximum recommended dose is 50mg (=5ml) of chloroprocaine hydrochloride.

The duration of action is dose-dependent

Special populations

The clinician's experience and knowledge of the patient's physical status are of importance when deciding the dose. It is advisable to reduce the dose in patients in a compromised general condition.

In addition, in patients with established concomitant disorders (e.g. vascular occlusion, arteriosclerosis, diabetic polyneuropathy) a reduced dose is indicated.

Paediatric population

The safety and efficacy of Ampres in children and adolescents have not been established. No data are available (see section 5.1).

Method of administration

For intrathecal use.

Ampres should be injected via the intrathecal route into the intervertebral space L2/L3, L3/L4 and L4/L5.

The entire dose should be injected slowly, after having aspirated a minimum quantity of CSF to confirm the correct position. The patient's vital functions should be checked extremely carefully maintaining continuous verbal contact.

For single use.

The medicinal product has to be visually inspected prior to use. Only clear solutions practically free from particles should be used. The intact container must not be re-autoclaved.

4.3 Contraindications

- hypersensitivity to the active substance, medicinal products of the PABA (para-aminobenzoic acid) ester group, other ester-type local anaesthetics or to any of the excipients listed in section 6.1,
- general and specific contra-indications to spinal anaesthesia regardless of the local anaesthetic used, should be taken into account (e.g. decompensated cardiac insufficiency, hypovolemic shock),
- intravenous regional anaesthesia (the anaesthetic agent is introduced into the limb and allowed to set in while tourniquets retain the agent within the desired area),
- serious problems with cardiac conduction,
- severe anaemia,
- patients taking anticoagulants or with congenital or acquired bleeding disorder.

4.4 Special warnings and precautions for use

Some patients require special attention in order to reduce the risk of serious undesirable effects, even when locoregional anaesthesia constitutes the optimum choice for the surgical intervention:

- Patients with total or partial heart block, since local anaesthetics can suppress myocardial conduction,
- Patients with high grade cardiac decompensation,
- Patients with advanced liver or kidney disease,
- Elderly patients and patients in poor general condition,

- Patients treated with class III antiarrhythmic agents (e.g. amiodarone). These patients should be subjected to careful observation and ECG monitoring, since cardiac effects may be observed (see section 4.5),
- In patients with acute porphyria, Ampres should only be administered when there is a compelling indication for its use, as Ampres may potentially precipitate porphyria. Appropriate precautions should be taken in all patients with porphyria,
- Since ester-type local anaesthetics are hydrolysed by plasma cholinesterase produced by the liver, chloroprocaine should be used cautiously in patients with advanced hepatic disease,
- Patients with genetic deficiency of plasma cholinesterase.

Ensuring the presence of reliable venous access is mandatory.

In high risk patients, the recommendation is to improve their general condition prior to the intervention.

A rare, but serious, undesirable effect of spinal anaesthesia is high or total spinal block, with consequent cardiovascular and respiratory depression. Cardiovascular depression is induced by an extended block of the sympathetic nervous system, which may induce severe hypotension and bradycardia to the point of cardiac arrest. Respiratory depression is induced by the block of the respiratory musculature and the diaphragm.

Especially in elderly patients there is an increased risk of high or total spinal block: consequently it is advisable to reduce the anaesthetic dose.

Particularly in the case of elderly patients, an unexpected drop in arterial pressure may occur as a complication of spinal anaesthesia.

Rarely, neurological damage may occur after spinal anaesthesia, manifesting as paraesthesia, loss of sensitivity, motor weakness, paralysis, cauda equina syndrome and permanent neurological injury. Occasionally these symptoms persist.

There is no suspicion that neurological disorders, such as multiple sclerosis, hemiplegia, paraplegia or neuromuscular disorders may be negatively influenced by spinal anaesthesia. Nevertheless, it should be used with care. Careful evaluation of the risk-benefit ratio is recommended prior to treatment.

In case of unintentional intravascular injection severe systemic toxicity may occur immediately (see section 4.9).

This medicinal product contains less than 1 mmol sodium (23 mg) per dose (maximum dose equal to 5 ml of Ampres), i.e. essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent administration of vasopressors (e.g. for the treatment of hypotension related to obstetric blocks) or ergot-type oxytocic medicinal product may cause severe, persistent hypertension or cerebrovascular accidents.

The para-aminobenzoic acid metabolite of chloroprocaine inhibits the action of sulfonamides. Therefore, chloroprocaine should not be used in any condition in which a sulfonamide medicinal product is being employed.

No studies have been performed on interactions between chloroprocaine and class III antiarrhythmics (e.g. amiodarone), but care must also be taken in this case (also see section 4.4).

The combination of various local anaesthetics induces additional effects which affect the cardiovascular system and the CNS.

4.6 Fertility, Pregnancy and lactation

Pregnancy

Animal studies are insufficient with respect to effects on pregnancy and foetal development (see 5.3).

Therefore, Ampres is not recommended during pregnancy and in women of childbearing potential not using contraception. The use of Ampres in pregnancy should only be considered if the expected benefit to the mother outweighs any potential risk to the foetus. This does not preclude the use of Ampres at term for obstetrical anaesthesia.

Breast-feeding

It is not known whether chloroprocaine/metabolites are excreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Ampres therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No fertility studies have been performed.

4.7 Effects on ability to drive and use machines

Ampres has major influence on the ability to drive and use machines

The doctor is responsible for deciding in each individual case if the patient can drive or use machines.

4.8 Undesirable effects

Summary of safety profile

The possible undesirable effects due to the use of Ampres are generally similar to the undesirable effects of other local anaesthetics for spinal anaesthesia from the ester group. The undesirable effects induced by the medicinal product are difficult to distinguish from the physiological effects of the nerve block (e.g. reduction in arterial pressure, bradycardia, temporary urine retention), from direct effects (e.g. spinal hematoma) or the indirect effects (e.g. meningitis) of the injection or from the effects due to the loss of cerebrospinal fluid (e.g. post-spinal headache).

Tabulated summary of adverse reactions

The adverse reactions listed below in Table 1 are classified according to System Organ Class. The frequency of undesirable effects listed below is defined using the following convention:
Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000), Not known (cannot be estimated from the available data).

Table 1 – Adverse reactions

Very common	Common	Uncommon	Rare	Very Rare
Immune system disorders				
			allergic reactions as a result of sensitivity to the local anaesthetic: characterized by signs such as urticaria, pruritus, erythema, angioneurotic oedema with possible airway obstruction (including laryngeal oedema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and possibly, anaphylactoid type symptomatology (including severe	

			hypotension)	
Injury, Poisoning and Procedural Complications				
	anaesthetic complication.			
Nervous system disorders				
	anxiety, restlessness, paraesthesia, dizziness	signs and symptoms of CNS toxicity (backache, headache, tremors possibly proceeding to convulsions, convulsions, circumoral paraesthesia, feeling of numbness affecting the tongue, hearing problems, visual problems, blurred vision, shaking, tinnitus, speech problems, loss of consciousness).	neuropathy, drowsiness merging into unconsciousness and respiratory arrest, 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, arachnoiditis, persistent motor, sensory and/or autonomic (sphincter control) deficit of some lower spinal segments with slow recovery (several months), cauda equina syndrome and permanent neurological injury.	
Eye disorders				
			diplopia	
Cardiac disorders				
			arrhythmia, depression of the myocardium, cardiac arrest (the risk is increased by high doses or unintended intravascular injection).	
Vascular disorders				
hypotension		bradycardia, hypertension, hypotension raised by high doses.		
Respiratory, thoracic and mediastinal disorders				
			respiratory depression	
Gastrointestinal disorders				
nausea	vomiting			

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

It is unlikely that Ampres, at the recommended posology by intrathecal administration, will induce plasma levels capable of inducing systemic toxicity.

Acute systemic toxicity

Systemic undesirable effects are of methodological (due to use), pharmacodynamic or pharmacokinetic origin and concern the central nervous system and the cardiocirculatory system.

Iatrogenic undesirable effects occur:

- after injecting an excessive quantity of solution,
- from accidental injection into a vessel,
- from incorrect patient position,
- from high spinal anaesthesia (marked drop in arterial pressure).

In the case of accidental intravenous administration, the toxic effect occurs within 1 minute. The intravenous LD50 of chloroprocaine HCl is 97 mg/kg in mice, 65 mg/kg in guinea pigs and <30 mg/kg in dogs, corresponding to human equivalent doses of 7.9 mg/kg, 14.1 mg/kg and < 16.7 mg/kg, respectively. The subcutaneous LD50 of chloroprocaine HCl in mice is 950 mg/kg, corresponding to human equivalent dose of 77.2 mg/kg.

Signs of overdose can be classified into two different sets of symptoms which differ in terms of quality and intensity.

Symptoms affecting the central nervous system

Generally, the first symptoms are paraesthesia in the mouth area, feeling of numbness of the tongue, feeling dazed, problems with hearing and tinnitus. Visual problems and muscle contractions are more severe and precede a generalized convulsion. These signs must not be mistaken for neurotic behaviour. Subsequently loss of consciousness and tonic-clonic seizure may occur, generally lasting between a few seconds and a few minutes. The convulsions are immediately followed by hypoxia and increased levels of carbon dioxide in the blood (hypercapnia), attributable to increased muscular activity associated with respiratory problems. In serious cases

respiratory arrest may occur. Acidosis and/or hypoxia potentiate the toxic effects of local anaesthetics.

The reduction or improvement of symptoms affecting the central nervous system can be attributed to the redistribution of local anaesthetic outside the CNS, with its consequent metabolism and excretion. Regression may be rapid, unless enormous quantities have been used.

Cardiovascular symptoms

In serious cases cardiovascular toxicity may occur. Hypotension, bradycardia, arrhythmia and also cardiac arrest may occur in the presence of a high systemic concentration of local anaesthetics.

The first signs of toxic symptoms affecting the central nervous system generally precede toxic cardiovascular effects. This statement does not apply if the patient is under general anaesthesia or heavily sedated with medicinal products such as benzodiazepine or barbiturates.

Treatment of acute systemic toxicity

The following measures must be taken immediately:

- Administration of Ampres must be stopped,
- An adequate supply of oxygen must be ensured: the airways should be kept clear, O2, should be administered, artificial ventilation (intubation) if required,
- In case of cardiovascular depression circulation must be stabilised.

If convulsions occur and do not resolve spontaneously after 15-20 seconds, the administration of an intravenous anticonvulsant is recommended.

Analeptics with a central action are contraindicated in the case of intoxication caused by local anaesthetics.

In the event of serious complications, when treating the patient it is advisable to obtain the assistance of a doctor specializing in emergency medicine and resuscitation (e.g. anaesthetist).

In patients with genetic deficiency of plasma cholinesterase an intravenous lipid solution could be administered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anaesthetics, local; esters of aminobenzoic acid

ATC code: N01BA04

Chloroprocaine, is an ester-type local anaesthetic. Chloroprocaine, blocks the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse and by reducing the rate of rise of the action potential.

The onset of action for spinal administration is very rapid (9.6 min ± 7.3 min at 40 mg dose; 7.9 min ± 6.0 min at 50 mg dose) and the duration of anaesthesia may be up to 100 minutes.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Ampres in all subsets of the paediatric population for spinal anaesthesia.

5.2 Pharmacokinetic properties

Absorption and Distribution

The plasma concentration should be negligible for intrathecal use.

Biotransformation

Chloroprocaine is rapidly metabolized in plasma by hydrolysis of the ester linkage by pseudocholinesterase. This process could be decelerated in case of pseudocholinesterase deficiency.

The hydrolysis of chloroprocaine results in the production of ß-diethylaminoethanol and 2-chloro-4-aminobenzoic acid.

The in vitro plasma half-life of chloroprocaine in adults is 21 ± 2 seconds for males and 25 ± 1 seconds for females. The in vitro plasma half-life in neonates is 43 ± 2 seconds. In women, plasma half-lives in vivo of 3.1 ±1.6 minutes was measured.

Elimination

The metabolites, ß-diethylaminoethanol and 2-chloro-4-aminobenzoic acid, are excreted by the kidney into the urine.

Pharmacokinetics in the spine

Elimination of chloroprocaine from the CSF is entirely by diffusion and vascular absorption, either in neural tissues in the intrathecal space or by crossing the dura

along the concentration gradient between CSF and the epidural space. Consequently, chloroprocaine is subject to vascular absorption. The predominant factors determining the rate of absorption are local blood flow and competing binding to local tissues, but not enzymatic hydrolysis in the CSF. In patients with cholinesterase deficiency it is reasonable to expect very low peak plasma levels of chloroprocaine after intrathecal injection. Clearance of chloroprocaine from CSF by diffusion across the dura into the epidural space and subsequent systemic absorption may not be impaired to a clinically significant degree.

5.3 Preclinical safety data

Concerning acute toxicity of 2-chloroprocaine following intravenous application see section 4.9.

Preclinical studies have been conducted in the case of spinal administration. Adverse effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

No studies in animals to evaluate carcinogenic potential and reproductive and developmental toxicity have been conducted with chloroprocaine.

In vitro genotoxicity studies did not provide evidence for 2-chloroprocaine to have a relevant mutagenic or clastogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid 3.7% (for pH adjustment)

Sodium chloride

Water for injection

6.2 Incompatibilities

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

6.3 Shelf life

2 years.

The medicinal product has to be used immediately after first opening

6.4 Special precautions for storage

Do not store above 25°C. Do not refrigerate or freeze. Keep ampoule in the outer carton, in order to protect from light.

6.5 Nature and contents of container

Type I clear colourless glass ampoule.

Box of 10 ampoules each containing 5 ml of solution for injection.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

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