Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ampres 20 mg/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution for injection contains 20 mg of chloroprocaine hydrochloride
1 vial with 20 ml solution, contains 400 mg of chloroprocaine hydrochloride

Excipients with known effect:
1 ml of solution contains 1.85 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 2.7 and 4.0.
The osmolality of the solution is comprised between 250 – 300 mOsm/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Perineural anaesthesia (peripheral nerve block) in adults for short-duration surgeries (not exceeding 60 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 treat the undesirable effects and complications of the procedure.

Posology
The duration of action of chloroprocaine is dose-dependent, the smallest dose required to produce an effective block should be used. Posology must be established on an individual basis and varies with the anaesthetic procedure, the vascularity of the tissues, the depth of anaesthesia and degree of muscle relaxation required, the duration of anaesthesia desired, and the physical condition of the patient.
When determining the dose, concomitant administration of other medicinal products should be taken into consideration.
The following table is a guide to dosage for the more commonly used blocks

Posology Adults

Anaesthetic Procedure	Volume (ml)	Total dose (mg)
Major Nerve Blocks*	15-40	300-800
Axillary block	20	400
Brachial plexus block	30-40	600-800
Femoral block	15-30	300-600
Sciatic block	20-30	400-600

Minor Nerve Blocks	0.5-5	10-100
Peribulbar block	5	100
Infraorbital block	0.5-1	10-20

*With regard to major nerve block, only for axillary block a dose recommendation can be given. There is presently no experience of specific dose recommendations for other blocks and the posology must be established on an individual basis.

The maximum recommended dose in adults is 11 mg/kg, but should not exceed the total dose of 800 mg (=40 ml) of chloroprocaine hydrochloride.

Special population
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, for elderly patients, 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 Perineural use (peripheral nerve block).

For single use only.
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 perineural anaesthesia (PNBs) regardless of the local anaesthetic used, should be taken into account
- intravenous regional anaesthesia (the anesthetic agent is introduced into the limb and allowed to set in while tourniquets retain the agent within the desired area)
- hypovolemia
- serious problems with cardiac conduction.

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 damage.
- Elderly patients and patients in poor general condition.
- Patients treated with class III antiarrhythmic medicinal products (e.g. amiodarone). These patients should be subjected to careful observation and ECG monitoring, since cardiac effects may be added (see section 4.5).
- 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.

Caution is required to prevent injections in inflamed areas.

In case of unintentional intravascular injection severe systemic toxicity may occur immediately (see sections 4.8 and 4.9)

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

A rare, but serious, undesirable effect of loco-regional anaesthesia (PNBs) is the peripheral nerve injury caused by an inadvertent damage to anatomic structures by the advancing needle. Most injuries are transient and often subclinical, or present as mild mononeuropathies. Rarely, injuries can result in permanent nerve damage.

Intra-articular infusions of local anaesthetics following arthroscopic and other surgical procedures is an unapproved use, and there have been post-marketing reports of chondrolysis in patients receiving such infusions.

Use in Ophthalmic Surgery: when local anesthetic injections are employed for retrobulbar block, lack of corneal sensation should not be relied upon to determine whether or not the patient is ready for surgery. This is because complete lack of corneal sensation usually precedes clinically acceptable external ocular muscle akinesia.

Chloroprocaine and its metabolites are known to be substantially excreted by the kidney, and the risk of toxic reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it may be useful to monitor renal function.

This medicinal product contains 37 mg sodium per 20 ml vial, equivalent to 1.85% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interactions

Concurrent administration of vasopressors (e.g. for the treatment of hypotension related to obstetric blocks) and ergot-type oxytocic medicinal products 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.
Concurrent use of cholinesterase inhibitors such as antimyasthenics, cyclophosphamide, echotiophate may inhibit the metabolism of chloroprocaine leading to increased risk of toxicity.

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.

Breastfeeding
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 the 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 regional anaesthesia from the ester group. These undesirables effects are generally dose related and may result from rapid absorption from the injection site, diminished tolerance, or from unintentional intravascular injection of the local anaesthetic solution. In addition to systemic dose-related toxicity, unintentional subarachnoid injection of drug during the intended performance of nerve blocks near the vertebral column (especially in the head and neck region) may result in underventilation or apnea ("Total Spinal"). 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), from direct effects (e.g. nerve injury) or the indirect effects (e.g. nerve inflammation) of the needle puncture.

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 edema with possible airway obstruction (including laryngeal edema), 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, paresthesia, dizziness	signs and symptoms of CNS toxicity (tremors possibly proceeding to convulsions, convulsions, circumoral paresthesia, 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, loss of bladder and bowel control, and loss of perineal sensation and sexual function and permanent neurological injury	

Eye disorders				
			diplopia	
Cardiac disorders				
		bradycardia.	arrhythmia, depression of the myocardium, cardiac arrest (the risk is increased by high doses or unintended intravascular injection).	
Vascular disorders				
hypotension.		hypertension, hypotension raised by high doses.		
Respiratory, thoracic and mediastinal disorders				
			dyspnoea.	
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 HPRA Pharmacovigilance, Website: www.hpra.ie

4.9 Overdose

It is unlikely that Ampres, at the recommended posology by perineural administration, will induce plasma levels capable of inducing systemic toxicity (see section 5.2).

A*cute 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.

In the case of accidental intravenous administration, the toxic effect occurs within 1 minute. The intravenous LD_{50} 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 paresthesia 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 erroneously 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, O_2 should be administered, artificial ventilation (intubation) if required.
- In case of cardiovascular depression circulation must be stabilized.

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 perineural administration is very rapid (6 to 12 min) and the duration of anaesthesia may be up to 100 minutes.
Patients with a successful block without any supplementation in the first 45 minutes after readiness for surgery are 90.8% with Chloroprocaine HCl.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with Ampres in all subsets of the paediatric population in perineural anaesthesia (peripheral nerve block) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption and Distribution
The plasma concentration should be negligible for perineural 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.

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 didn't provide evidence for 2-chloroprocaine and 4-amino-2-chlorobenzoic acid (main metabolite) 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 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

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 the vial in the outer carton, in order to protect from light.

6.5 Nature and contents of container

Type I clear colourless glass 20 ml vial.
Vials closures are bromobutyl stoppers and seals used are aluminium flip-off caps.
Box of 1 vial containing 20 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

B. Braun Melsungen AG
Carl-Braun-Straße 1
34212 Melsungen
Germany

8 MARKETING AUTHORISATION NUMBER

PA0736/043/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26th June 2020
Date of last renewal: 19th March 2022

10 DATE OF REVISION OF THE TEXT

January 2022