SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cocaine Hydrochloride Solution 10% w/v.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cocaine Hydrochloride Ph Eur 10% w/v.

3. PHARMACEUTICAL FORM

Sterile oromucosal solution 10% w/v
Sterile nasal spray, solution 10% w/v

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cocaine Hydrochloride Solution is indicated to provide local anaesthesia and vasoconstriction of accessible mucous membranes prior to surgery especially in the oral, laryngeal, and nasal cavities. Vasoconstriction prevents excessive blood loss and reduces obstruction/restriction of the operative field.

4.2 Posology and method of administration

For topical use only. Not for injection or to be taken.

The maximum total dose recommended for application to the mucosa in fit adults is 1.5mg/Kg.

It should be used only by those skilled in the precautions needed to minimise absorption and the consequent risk of arrhythmias.(see section on Precautions)

Method of Administration

Adults

Prime the pump dispenser by activating the pump 3 times.

The concentration of the cocaine hydrochloride solution is 100mg/ml. The dispenser contains only 2.5ml of solution.

One spray delivers 130µl of solution (containing 13mg of Cocaine). Therefore, a maximal dose of 1.5mg/Kg of cocaine (approx. 1ml of 10% solution), is equivalent to approximately 8-9 sprays for a 70Kg adult, and this dose must **not** be exceeded.

Any remaining solution should be returned to the pharmacy.

Children

Cocaine hydrochloride solution should not be administered to children .

Elderly

Cocaine hydrochloride solution should not be administered to the elderly .

Indications from some studies of medicinal cocaine show that death can ensue from 0.8-1.0g (8-10ml of a 10% w/v solution of cocaine).
Some persons have a cocaine idiosyncrasy and death may occur quite suddenly after doses of only 20mg.

The patient must be monitored for any signs or symptoms of toxicity during and after administration of cocaine. The appropriate treatment **must** be available and medical equipment **must** be ready for use at all times.

4.3 Contraindications

Cocaine hydrochloride is largely (90%) metabolised by cholinesterase, thus those patients taking cholinesterase inhibitors such as Ecothiopate eye drops for the treatment of glaucoma, or neostigmine for the treatment of Myasthenia Gravis, or those patients with hereditary Pseudocholinesterase deficiency, should not be administered cocaine hydrochloride. If these patients are given cocaine hydrochloride, higher blood levels result, with a greater risk of drug toxicity.

Adrenaline is believed to enhance the toxic effects of cocaine by further increasing the level of circulating catecholamines, and thus should not be used in association. Other sympathomimetic drugs are thus also contra-indicated. Cocaine hydrochloride's use is also contra-indicated in patients receiving α-modifying drugs such as guanethidine sulphate, reserpine and tricyclic anti-depressants; as these drugs also increase the activity of the sympathetic nervous system.

Cocaine is contra-indicated in patients with epilepsy because it lowers the seizure threshold.

Cocaine should be avoided in Porphyria, as it has been shown to be porphyrinogenic in animals or in vitro systems, thus exacerbating the disorder.

4.4 Special warnings and precautions for use

Indications from some studies of medicinal cocaine show that death can ensue from 0.8-1.0g (8-10ml of a 10% w/v solution of cocaine).

Some persons have a cocaine idiosyncrasy and death may occur quite suddenly after doses of only 20mg.

Cocaine should not be applied to damaged mucosa or open wounds because of the risk of systemic toxicity from enhanced absorption.

Cocaine should be used with caution in patients with hypertension, cardiovascular disease or thyrotoxicosis because the vasoconstriction and tachycardia may reduce cardiac oxygenation while increasing oxygen demand It should also be used with caution in patients with diabetes because cocaine sensitises the person to adrenaline which mobilises glucose and causes blood glucose levels to go out of control.

At high doses cocaine depresses the respiratory centres and thus should be cautiously employed in combination with other respiratory depressants (e.g. opiates, barbiturates, alcohol).

The use of cocaine in the elderly is not recommended because of the risk of vasoconstriction and tachycardia. Cocaine is also not recommended in children, or in pregnancy or lactation.

Overall, the patient's condition, the appropriate dose and method of administration must all be considered prior to the application of cocaine. The initial signs and symptoms of cocaine toxicity and the appropriate treatment required to combat toxicity must be known to the surgeon or anaesthetist.

4.5 Interactions with other medicinal products and other forms of interaction

Cholinesterase Inhibitors.

e.g. Ecothiopate eye drops for the treatment of Glaucoma, and neostigmine for the treatment of Myasthenia Gravis.

If these drugs are administered to patients receiving cocaine, higher blood levels result, with a greater risk of drug toxicity. (See Contra-indications)

Adrenaline and other sympathomimetics.

Adrenaline is believed to enhance the toxic effects of cocaine by further increasing the level of circulating catecholamines. (See Contra-indications)

Ephedrine is used in the treatment of reversible airways obstruction and is present in some cough linctus preparations. Amphetamines (CNS stimulants) have some similar actions to sympathomimetics..

Monoamine-Oxidase Inhibitors.

Cocaine potentiates the effects and toxicity of MAO inhibitors, e.g. phenelzine or isocarboxazid.

α-Modifying Drugs.

e.g. guanethidine sulphate and reserpine, both used in the treatment of hypertension; and tricyclic anti-depressants such as imipramine and amitriptyline. These drugs also increase the activity of the Sympathetic Nervous System, which is also increased by administration of cocaine.

Halothane.

Maintenance of anaesthesia with halothane, a volatile anaesthetic agent, may augment any interaction between cocaine and catecholamines by sensitising the myocardium. However, deeper levels of general anaesthesia inhibit adrenal release of catecholamines and may conversely decrease the potential arrhythmogenic effects.
Cholinesterase Inhibitors.

4.6 Pregnancy and lactation

Cocaine is not recommended for use during pregnancy and lactation.

Cocaine exposure early in pregnancy is reflected by cocaine and metabolite burden in the meconium, which is initially formed at the end of the first trimester, due to cocaine crossing the placenta.

Animal and autopsy studies indicate that the cocaine metabolite benzoylecgonine preferentially accumulates in foetal tissue. Recent human and animal studies suggest that the slowly eliminated metabolites of cocaine have significant physiological and behavioural properties. There is also an increased risk of spontaneous abortion and other birth complications due to vasoconstriction by cocaine increasing maternal blood pressure and reducing placental blood flow.

The following signs and symptoms are typical of babies born following cocaine use by the mother during pregnancy : irritability, inconsolability, hypertoxicity, tremulousness, hyperactive moro reflex, sneezing or yawning,

lethargy, suck reflex, high pitched cry, poor feeding, poor weight gain, fever, diarrhoea, spitting or vomiting, tachypnoea, tachycardia, skin abrasions and respiratory distress. Cocaine is also excreted in breast milk.

4.7 Effects on ability to drive and use machines

Due to the pharmacological actions of cocaine, it is recommended that patients who have been administered cocaine do not drive or operate machinery.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
    - The medicine has been prescribed to treat a medical or dental problem and
    - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
    - It was not affecting your ability to drive safely

4.8 Undesirable effects

Cocaine may cause restlessness, excitement, euphoria, garrulousness and increased motor activity. With high doses or repeated use, confusion, paranoia, hallucinations, altered tactile sensations and psychosis have been reported. Seizures can occur, perhaps due to lowering of the seizure threshold, or hyperpyrexia, or due to life threatening cardiac arrhythmias.

Cocaine directly causes a rise in body temperature by increasing heat production through stimulated muscle activity, and indirectly by causing vasoconstriction that decreases heat loss. A direct pyrogenic effect may be caused by cocaine's direct effect on thermoregulatory centres in the hypothalamic area.

Low doses of cocaine in humans do not change respiratory rate or depth, but at higher doses a CNS mediated increase in respiratory rate and decrease in tidal volume is described.

A migraine-like headache may be the result of cocaine induced vascular changes. Adrenergic stimulation may cause intensive hypertension, due to tachycardia and peripheral vasoconstriction. Cocaine increases cardiac

activity, which raises oxygen demand within myocardial tissue. Other signs of adrenergic excess seen with cocaine include mydriasis, diaphoresis, tremor, hyperactive bowel sounds and hyperreflexia. Vasoconstriction due to cocaine may also produce ischaemia in the fingers, toes, spinal cord, kidneys, spleen, and intestines.

Cocaine suppresses Rapid Eye Movement (REM) sleep and total sleep. In low doses cocaine has an anorexic effect.

4.9 Overdose

The signs and symptoms of overdose must be known to the otolaryngologist or anaesthetist administering cocaine topically.

Toxicity first occurs as an overstimulated excited state. The toxic reaction may progress to convulsions, loss of consciousness, respiratory and cardiovascular depression or arrest, and death.

Toxicity may arise from any route of cocaine administration. Clinically, otolaryngologists reported a higher percentage of untoward reactions when cocaine was applied to the tracheobronchial tree rather than the nasal mucosa.

Symptoms of acute toxicity include delirium, tremor, massive convulsions and a direct cardiotoxic effect due to its sympathomimetic effect.

Controlled clinical studies have been performed examining the dose-response effects from intranasal (snorting) administration of cocaine. At 10mg no observable subjective or physiological effects were apparent; at 25mg there was an increase in systolic blood pressure and mild euphoria reported as relaxation; at 100mg, heart rate and diastolic blood pressure were increased and a strong feeling of euphoria was present. These effects were short-lasting and lethargy and irritability as an after-effect were reported by a few subjects within one hour after a cocaine administration.

The LD_{50} (lethal dose that is fatal in 50% of cases) of cocaine in adults is estimated to be 500mg after oral administration.

A fatal dose of cocaine is about 0.8-1g for an adult. This is the amount contained in 8-10ml of a 10% w/v cocaine solution. This must be emphasised in order to appreciate the potency and danger of this cocaine solution.

On an acute basis, cocaine can prolong the time to reach orgasm in men and women.

Cocaine use by pregnant women can interfere with gestation and produce abnormalities, possibly permanent, in their children. (See Pregnancy And Lactation)

At clinical doses, cocaine has little general toxicity, when applied locally and for a short period of time.

Treatment of Overdose :

If a cocaine-impregnated pledget is still in the nose when toxicity occurs, it must be promptly removed. Seizures, and cardiovascular and respiratory collapse in the late stages have been treated with respiratory support, anti-convulsants, and cardiotonic drugs.

The treatment of acute poisoning by cocaine should include the removal of any remaining drug from the mucosal surface by rinsing with tap water or normal saline.

In a medical setting where cocaine is used, positive-pressure breathing equipment should be functional and easily accessible, and intravenous diazepam should be immediately available.

Intravenous pentobarbital is a more stable preparation; it is slower acting but can be used if diazepam is not available.

Steps in the Management of Cocaine Overdose.

Prevent convulsion :	At first sign of excitability (talkative stage), administer: diazepam injectable 5mg/ml 1-2ml intravenously in patients aged 5 years to adult
Hypertension :	labetalol, phentolamine or sodium nitroprusside (not propranolol since it potentiates cocaine toxicity - see below∗)
Psychiatric reactions :	Delusions may respond to neuroleptics (phenothiazine and butyrophenone) but these agents also may increase the chance of seizures; benzodiazepines may be useful in reducing anxiety.
Respiratory support :	After convulsion or if apnoeic or if Cheyne-Stokes respiration: Positive pressure ventilation - mouth to mouth, bag and mask, endotracheal
Cardiac resuscitation and anti-arrhythmics :	In massive overdosage

∗ Propranolol has been used to treat cocaine-induced hypertension and arrhythmias but, following a report of paradoxical hypertension presumably due to unopposed α-adrenergic stimulation, a beta-blocker with both α- and β-adrenergic effects such as labetalol is now preferred by some for hypertension; sodium nitroprusside, or phentolamine may also be used.

However, one must be aware that like propranolol, labetalol may worsen hypertension in patients with hyperadrenergic states, because the β-blocking properties of labetalol are much more potent than its α-blocking properties. Like propranolol, labetalol has the potential to cause a state of relatively unopposed α-effect, thereby raising the blood pressure. If such a complication ensues, treatment with a pure α-blocker such as phentolamine, or a vasodilator such as nitroprusside, diazoxide, or possibly nifedipine is indicated. It has been found that esmolol, an ultra short-acting β_1 - selective adrenergic blocker with an elimination half-life of about 9 minutes, is an attractive choice for the treatment of a cocaine-induced hyperadrenergic state, because the β_1 - selectivity rendered hypertension or coronary artery spasm from unopposed α-adrenergic tone is less of a risk than with non-selective β-blocking drugs.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Cocaine has two distinct pharmacological actions:

- a local anaesthetic effect and
- a central nervous system stimulation

This drug produces its local anaesthetic effects by inhibiting the permeability of the cell membrane to sodium ions during depolarisation, thus blocking the initiation and conduction of electrical impulses within nerve cells. Its actions on the central nervous system involve the alteration of several neurotransmitters. Cocaine affects the sympathetic nervous system by blocking the re-uptake of noradrenaline and dopamine. This initially causes cortical stimulation and may result in restlessness, excitement, euphoria, garrulousness, and increased motor activity. Confusion, paranoia, hallucinations, altered tactile sensations, and psychosis have also been reported, especially with high doses or repeated use. Seizures can occur, perhaps due to lowering of the seizure threshold, due to cocaine-induced hyperpyrexia, or due to life threatening cardiac arrhythmias. Cocaine directly causes a rise in body temperature by increasing heat production through stimulated muscle activity, and indirectly by causing vasoconstriction that decreases heat loss. A direct pyrogenic effect may be caused by cocaine's direct effect on thermoregulatory centres in the hypothalamic area.

Respiratory Effects:- Cocaine initially stimulates the respiratory centre, resulting in increased respiratory rate. However, the depth of respiration is soon decreased to a rapid and shallow pattern. This may be followed by depression of the medullary centres, causing respiratory failure. Cocaine's effects on the lungs and respiration can also result in metabolic acidosis or alkalosis. The respiratory effects of Cocaine appear to be dose related. Low doses in humans do not change respiratory rate or depth, but at higher doses a

CNS mediated increase in respiratory rate and decrease in tidal volume is described. At very large cocaine doses, Cheyne-Stokes respirations and apnoea occur.

Cerebrovascular effects:- Cocaine can reduce blood flow within the brain. A migraine-like headache may be the result of cocaine induced vascular changes. Other complications include cerebral haemorrhage or infarction, most likely related to sudden intensive hypertension resulting from adrenergic stimulation. In the central nervous system, cocaine suppresses both rapid eye movement (REM), sleep and total sleep. In low doses, cocaine has an anorexic effect.

Cardiovascular effects:- The initial effect of cocaine on the cardiovascular system is bradycardia, which is short-lived and followed by tachycardia that results from central and peripheral stimulatory effects. The tachycardia and intense peripheral vasoconstriction result in hypertension. Ventricular premature contractions, ventricular tachycardia and fibrillation, asystole, and myocardial infarction have also been reported. In cocaine induced acute myocardial infarction, cocaine increases cardiac activity, which raises oxygen demand within myocardial tissue. Cocaine simultaneously produces vasoconstriction of coronary arteries. Thus when cardiac tissue requires increased oxygenation, cocaine induced vascular changes prevent it. Other signs of adrenergic excess seen with cocaine include mydriasis, diaphoresis, tremor, hyperactive bowel sounds and hyperreflexia. Vasoconstriction due to cocaine may also produce ischaemia in the fingers, toes, spinal cord, kidneys, spleen, and intestines.

Reproductive effects:- On an acute basis, cocaine can prolong the time to reach orgasm in men and women.

Cocaine use by pregnant women can interfere with gestation and produce abnormalities, possibly permanent, in their children. (See Pregnancy And Lactation)

5.2 Pharmacokinetic properties

Cocaine is metabolised in humans by two major pathways. The first accounts for over 90% of the transformation and involves various hydrolytic reactions. The second is an oxidative process. The hydrolytic pathway is catalysed by serum and liver pseudocholinesterase which produces ecgonine methyl ester, benzoylecgonine and ecgonine. The minor oxidative route appears to be responsible for the hepatotoxicity. Cocaine is N-demethylated to produce norcocaine which is then rapidly oxidized to N-hydroxynorcocaine, which in turn is further metabolised producing norcocaine nitroxide. The latter is believed to be ultimately responsible for the hepatotoxicity elicited by cocaine.

Absorption from mucous membranes is delayed by vasoconstriction, and peak plasma concentrations of up to 474ng/ml have been obtained 15-120 minutes

after application of doses of 1.5 - 2mg per Kilogram bodyweight to the nasal mucosa as a 10% w/v cocaine hydrochloride solution.

Cocaine applied to the mucous membranes may be detectable for as long as three hours after its application. A true biological half-life for cocaine is difficult to ascertain, as serum concentrations reflect a dynamic balance between the absorption and degradation of cocaine, i.e. the concentration of cholinesterase in the blood can vary between individuals.

It is considered possible that topical application of cocaine to the nose or pharynx, may indeed implicate an unintentional oral administration of cocaine should a small quantity of the solution trickle down the back of the throat. It is thus necessary to consider the effect of an oral dose equivalent to the topical dose.

In a well controlled study after oral ingestion of cocaine, the plasma levels, objective findings and subjective effects all correlated with the levels after intranasal application.

A common misconception is that if taken orally, cocaine is rendered ineffective by gastric acidity.

Cocaine is not completely destroyed by hydrolysis in the stomach. When ingested orally, the gastrointestinal absorption is delayed, but at least 30% is estimated to be absorbed and bioavailable. Oral ingestion results in a lag time of 30 minutes before plasma levels can be detected. Peak plasma concentrations occur 50-90 minutes following ingestion and are similar to those after nasal application.

Absorption of cocaine may be enhanced where the skin is broken or where there is inflammation. In addition, absorption of cocaine from the mucosa varies in different parts of the respiratory tract. It has been found that absorption from the trachea is greater and more rapid than from the pharynx. Also, absorption is greater from the respiratory tract than from other mucous membranes.

The half life of cocaine in serum is dependent on the route of administration, and average values of 0.6 hour for intravenous administration, 0.9 hour for oral use, and 1.3 hours after intranasal have been quoted. However, these values must be interpreted with caution, as there is considerable variability between individuals and within individuals over time, and cocaine applied to the mucous membranes may be detectable in serum for as long as three hours after its application.

When applied to mucous membranes, surface anaesthesia develops rapidly and persists for 30mins or longer depending on the concentration of cocaine solution used, the dose, and on the vascularity of the tissue.

5.3. Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dilute Hydrochloric Acid
Water for Injections

6.2 Incompatibilities

Cocaine hydrochloride solution is incompatible with phenol, sodium borate and silver nitrate.

6.3 Shelf life

1 year

6.4 Special precautions for storage

Do not store above 25°C. Protect from light. Store in the original container and keep in the outer case.

6.5 Nature and contents of container

8ml type 1 clear glass bottle, with chlorobutyl rubber stopper and plastic screw cap, containing 2.5ml of a 10% w/v Cocaine Hydrochloride solution for topical application. A pump and actuator are included in the pack.

6.6 Instructions for use/handling

Ensure the dose used for each patient does not exceed 1.5mg/Kg (a volume of approximately 1ml, of a 10% w/v solution for a 70Kg adult). Any remaining solution must be returned to the pharmacy for disposal in the appropriate manner.

Not for multi-dose use.

7 MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

12064/0016

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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