AMENDED PROFESSIONAL INFORMATION (CLEAN COPY)

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

PHENYLCORD 10 mg/ml (Solution for injection)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml vial contains 10 mg phenylephrine hydrochloride.

For the full list of excipients, see section 6.1.

Excipient with known effect:

Contains sodium metabisulphite: 2 mg/ml

3. PHARMACEUTICAL FORM

Solution for injection

A clear, colourless solution filled in a clear glass vial. When examined under suitable conditions of visibility it should be practically free from foreign particles.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

PHENYLCORD 10 mg/ml is indicated for increasing the blood pressure in adults with clinically significant hypotension resulting primarily from vasodilation, in such settings as septic shock or anaesthesia.

The duration of action is short-lived (minutes) and repeat injections are frequently required.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

PHENYLCORD CAN ONLY BE ADMINISTERED VIA IV AFTER DILUTION

PHENYLCORD 10 mg/ml should only be administered by healthcare professionals with appropriate training and relevant experience in the safe administration of phenylephrine preparations.
PHENYLCORD 10 mg/ml should be administered in the lowest effective dosage for the shortest possible time. When possible, small doses should be injected initially and subsequent doses determined by pressor response.

Patients receiving PHENYLCORD 10 mg/ml should be closely monitored. Treatment with PHENYLCORD 10 mg/ml is not a substitute for replacement of blood, plasma, fluids and/or electrolytes. Prior to administration of therapy, hypovolaemia should be corrected. Acidosis may reduce the effectiveness of phenylephrine.

Posology

Adults

Intravenous bolus injection

10 mg of phenylephrine (1 ml of PHENYLCORD 10 mg/ml) must be diluted to 200 ml of glucose 5 % injection or sodium chloride 0,9 % injection prior to bolus intravenous injection. This dilution yields a final concentration of 50 µg/ml. Withdraw an appropriate dose from the 50 µg/ml solution prior to bolus intravenous administration of the diluted solution.

- *Dosing for perioperative setting*

  In adult patients undergoing surgical procedures with either neuraxial anaesthesia or general anaesthesia: 50 µg to 250 µg by intravenous bolus administration. The most frequently reported initial bolus dose is 50 µg or 100 µg.

Continuous infusion

10 mg of phenylephrine (1 ml of PHENYLCORD 10 mg/ml) must be diluted in 500 ml of glucose 5 % injection or sodium chloride 0,9 % injection prior to administration via intravenous infusion:

- *Dosing for perioperative setting*

  In adult patients undergoing surgical procedures with either neuraxial anaesthesia or general anaesthesia: 0,5 µg/kg/min to 1,4 µg/kg/min by intravenous continuous infusion, titrated to blood pressure goal.

- *Dosing for septic shock*

  In adult patients with septic shock: 0,5 µg/kg/min to 6 µg/kg/min by intravenous continuous infusion, titrated to blood pressure goal. Doses above 6 µg/kg/min do not show significant incremental increase in blood pressure.

Special populations

Patients with renal impairment

Lower doses of PHENYLCORD 10 mg/ml may be required in patients with renal impairment.

Patients with hepatic impairment

Higher doses of PHENYLCORD 10 mg/ml may be needed in patients with liver cirrhosis.

Elderly patients

Treatment of the elderly should be made with caution.

Paediatric population

PHENYLCORD 10 mg/ml should not be administered to paediatric patients (see Section 4.3).
The safety and efficacy of PHENYLCORD 10 mg/ml in children have not been established. No data are available.

Method of administration

PHENYLCORD 10 mg/ml should be administered by slow intravenous bolus injection or continuous intravenous infusion, after dilution.

When discontinuing therapy, the dosage should be reduced gradually, since sudden cessation of therapy may result in severe hypotension, intravascular fluid should be administered if necessary to avoid hypotension.

For further instructions on dilution and preparation of the injection see section 6.6.

4.3 CONTRAINDICATIONS

PHENYLCORD is contraindicated in:

- Hypersensitivity to phenylephrine hydrochloride or to any of the excipients of PHENYLCORD (see section 6.1)
- Paediatric use
- PHENYLCORD is contraindicated in the presence of severe:
    - Uncontrolled hypertension or peripheral vascular disease due to the risk of ischaemic gangrene or vascular thrombosis
    - Hyperthyroidism
    - Heart-block with or without bradycardia
    - Uncontrolled cardiac failure
    - Bradycardia (less than 50 bpm)
    - Seriously impaired coronary arterial circulation
- PHENYLCORD should not be used in combination with indirectly acting sympathomimetic medicines (ephedrine, methylphenidate, pseudoephedrine): risk of vasoconstriction and / or hypertensive crisis.
- PHENYLCORD should not be used in combination with alpha-sympathomimetic medicines (oral and / or nasal use) (etilefrine, midodrine, naphazoline, oxymetazoline, synephrine, tetryzoline, tuaminoheptane, tymazoline): risk of vasoconstriction and / or hypertensive crisis.

- PHENYLCORD should not be used in combination with non-selective monoamine oxidase inhibitors (MAOs) (or within two weeks of their withdrawal) due to the risk of paroxysmal arterial hypertension and possibly fatal hyperthermia (see section 4.5).
- Avoid in patients with prostatic enlargement.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Sustained IV infusion may result in diminished efficacy.

The arterial blood pressure should be monitored during treatment.

PHENYLCORD should be administered with care to patients with:

- Diabetes
- Arterial hypertension
- Aneurysm
- Uncontrolled hyperthyroidism
- Coronary heart disease and chronic heart disease
- Bradycardia
- Tachycardia
- Dysrhythmia
- Angina pectoris (phenylephrine can precipitate or exacerbate angina in patients with coronary artery disease and history of angina)
- Non-severe peripheral vascular insufficiency
- Closed angle glaucoma

Concurrent use of a halogenated volatile anaesthetic (e.g. desflurane, enflurane, halothane, isoflurane, methoxyflurane, sevoflurane) with phenylephrine as in PHENYLCORD, may increase the risk of perioperative hypertensive crisis and dysrhythmia (see section 4.5).

Severe bradycardia and decreased cardiac output may occur. Excessive peripheral and visceral vasoconstriction with ischaemia to vital organs may occur, especially in patients with extensive peripheral vascular disease e.g. Raynaud's phenomenon. Increased blood pressure may occur and precipitate underlying heart failure, angina in patients with severe arteriosclerosis or past history of angina, and increase pulmonary arterial pressure.
In patients with serious heart failure or cardiogenic shock, phenylephrine may cause deterioration in the heart failure as a consequence of the induced vasoconstriction (increase in afterload).
Therefore, care should be exercised in administering PHENYLCORD to patients with arteriosclerosis, the elderly and to patients with impaired cerebral or coronary arterial circulation.
Patients with medical conditions such as decreased cardiac output or peripheral or coronary artery disease should have frequent monitoring of vital body functions and lower systemic blood pressure boundary should be considered as a criterion for dose reduction or discontinuation of PHENYLCORD.

Particular attention should be paid during injection to avoid extravasation, since this may cause tissue necrosis.

Lower doses may be required in patients with renal impairment.

Higher doses may be required in patients with liver cirrhosis.

Blood pressure response to phenylephrine may be increased in patients with autonomic dysfunction.

The administration of PHENYLCORD simultaneously with the following medicines is not recommended, because of the risk of vasoconstriction and / or hypertensive crisis associated with its indirect sympathomimetic effect (see section 4.5):

- dopaminergic ergot alkaloids (bromocriptine, carbergoline, lisuride or pergolide) or vasoconstrictors (dihydroergotamine, ergotamine, or methysergide, methylergometrine).
- in combination with linezolid.

Concurrent use may prolong and intensify cardiac stimulation and vasopressor effects because of the release of catecholamines, which accumulate in intraneuronal storage sites during MAO inhibitor therapy; this may result in headache, cardiac dysrhythmias, vomiting or sudden and severe hypertensive or hyper-pyretic crises.

For patients who have been receiving MAO inhibitors 2 to 3 weeks prior to administration of sympathomimetic medicines, the initial dosage should be reduced to be no more than one-tenth of the usual dose.

Use of phenylephrine in patients with shallow anterior chamber, a history of acute narrow angle glaucoma and/or insufficient pupil dilation can increase the risk of both iridocele and floppy iris syndrome.

PHENYLCORD contains sodium metabisulphite, which may rarely cause severe hypersensitivity reactions and bronchospasm.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Contraindicated combinations (see section 4.3):

- Non-selective monoamine oxidase inhibitors (MAOIs) (iproniazid, nialamide, phenelzine): increased risk of paroxysmal hypertension, hyperthermia possibly fatal. Due to the long duration of action of MAOIs, this interaction is still possible 15 days after discontinuation of the MAOIs.
- Indirect sympathomimetics medicines (ephedrine, methylphenidate, pseudoephedrine): increased risk of vasoconstriction and / or hypertensive crisis.
- Alpha sympathomimetic medicines (oral and/or nasal use) (etilefrine, midodrine, naphazoline, oxymetazoline, synephrine, tetryzoline, tuaminoheptane, tymazoline): increased risk of vasoconstriction and / or hypertensive crisis.

Combinations not recommended (see section 4.4):

- Dopaminergic ergot alkaloids (bromocriptine, cabergoline, lisuride and pergolide): increased risk of vasoconstriction and/or hypertensive crisis.
- Vasoconstrictor ergot alkaloids (dihydroergotamine, ergotamine, methylergometrine, methysergide): increased risk of vasoconstriction and/or hypertensive crisis.
- Linezolid: increased risk of vasoconstriction and/or hypertensive crisis.
- Tricyclic antidepressants (desipramine, imipramine, nortriptyline): increased risk of paroxysmal hypertension with possibility of dysrhythmia (inhibition of adrenaline or noradrenaline entry in sympathetic fibres).
- Noradrenergic-serotoninergic antidepressants (venlafaxine): increased risk of paroxysmal arterial hypertension with possibility of dysrhythmias (inhibition of adrenaline or noradrenaline entry in sympathetic fibres).
- Selective monoamine oxidase inhibitors (MAOs) (moclobemide, pargyline, selegiline, toloxatan): risk of vasoconstriction and/or hypertensive crisis.
- Guanethidine and related products: substantial increase in blood pressure (hyperreactivity linked to the reduction in sympathetic tone and / or to the inhibition of adrenaline or noradrenaline entry in sympathetic fibres). If the combination cannot be avoided, use with caution lower doses of sympathomimetic medicines.
- Digoxin, quinidine: increased risk of dysrhythmias.
- Halogenated volatile anaesthetics (desflurane, enflurane, halothane, isoflurane, methoxyflurane, sevoflurane): risk of perioperative hypertensive crisis and dysrhythmia.
- The effect of antihypertensive and diuretic medicines used as antihypertensives may be reduced when used concurrently with PHENYLCORD; the patient should be carefully monitored to confirm the desired effect is obtained.

- Beta-adrenoceptor-blocking medicines, systemic or ophthalmic - concurrent use of PHENYLCORD may result in an exaggeration of the vasoconstriction effects and profound bradycardia.
- Reserpine and other sympatholytic medicines - concomitant use with PHENYLCORD causes a substantial increase in blood pressure. If the combination cannot be avoided, use with caution.
- The pressor effect of phenylephrine is increased in patients receiving atropine sulphate.

Combinations requiring caution:

- Oxytocic medicines: The effect of pressor-active sympathomimetic amines is potentiated. Thus, some oxytocic medicines may cause severe persistent hypertension and strokes can occur during post-partum period.
- Digoxin: PHENYLCORD may be used with digoxin for therapeutic advantage; caution and close electrocardiographic monitoring are recommended during concurrent use.
- Alpha-adrenoceptor-blocking medicines (doxazosin, labetalol, prazosin, haloperidol, phenothiazines): concurrent use may antagonise the peripheral vasoconstriction effect of PHENYLCORD.
- Caution should be applied when administering atomoxetine concurrently, as there is potential for synergistic pharmacological effects.
- The pressor effects of phenylephrine may be slightly reduced by lithium carbonate.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

The safety of PHENYLCORD during pregnancy has not been established. Animal studies are insufficient with respect to effects on pregnancy, embryonal / foetal development, parturition or postnatal development. The potential risk for humans is unknown.

Breastfeeding

The safety of PHENYLCORD during breastfeeding has not been established. Small amounts of phenylephrine are excreted in human milk. The administration of vasoconstrictors to the mother puts the child at risk for cardiovascular and neurological effects. PHENYLCORD should not be used during lactation.

Fertility

There are no data available regarding fertility, following treatment with phenylephrine.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Phenylephrine, as in PHENYLCORD, can cause undesirable effects (including hypotension with dizziness, fainting, dyspnoea, muscular weakness), which may affect the ability to drive and use machines.

Patients should be advised not to engage in driving or using machines until they know how PHENYLCORD might affect them.

4.8 UNDESIRABLE EFFECTS

Summary of the safety profile

Most of the adverse events of phenylephrine are dose-dependent and a consequence of the expected pharmacodynamic profile.

PHENYLCORD may cause a transient tingling and coolness of the skin and a temporary sensation of fullness in the head. Extravasation of the injection may cause local necrosis (see section 4.4).

Peripheral vasoconstriction, possibly leading to necrosis or gangrene, may occur with prolonged use of PHENYLCORD in high doses or low doses in the presence of peripheral vascular disease.

Tabulated list of adverse reactions

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTION
Immune system disorders	Less frequent	Hypersensitivity
Metabolic and nutrition disorders	Frequency unknown	Glucose metabolism abnormal, metabolic disorders
Psychiatric disorders	Less frequent	Euphoria, agitation, anxiety, psychotic states, confusion
Nervous system disorders	Frequent	Headache
	Less frequent	Tingling, fullness head, nervousness or restlessness, insomnia, paraesthesia, tremor
Eye disorders	Less frequent	Mydriasis, aggravation of pre-existing angle-closure glaucoma
Cardiac disorders	Less frequent	Anginal pain, reflex bradycardia, tachycardia, ventricular dysrhythmias
	Frequency unknown	Dysrhythmia, cardiac arrest, palpitations, myocardial ischemia
Vascular disorders	Less frequent	Cerebral haemorrhage, hypertension, hypotension

		with dizziness, hypertensive crisis, pallor
	Frequency unknown	Fainting, flushing, coldness of skin
Respiratory, thoracic and mediastinal disorders	Less frequent	Dyspnoea, pulmonary oedema
Gastrointestinal disorders	Less frequent	Nausea, vomiting
	Frequency unknown	Hypersalivation
Skin and subcutaneous tissue disorders	Less frequent	Piloerection, sweating, skin blanching
	Frequency unknown	Diaphoresis
Musculoskeletal and connective tissue disorders	Less frequent	Muscular weakness
Renal and urinary disorders	Less frequent	Difficulty in micturition and urinary retention
General disorders and administration site conditions	Less frequent	Extravasation necrosis at injection site

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 OVERDOSE

Symptoms of overdosage include headache, nausea, vomiting, hypertension (which may be severe), palpitations and reflex bradycardia and other cardiac dysrhythmias (ventricular extra systoles and short paroxysms of ventricular tachycardia). Treatment should consist of symptomatic and supportive measures.

Should an excessive elevation of blood pressure occur, the administration of PHENYLCORD should be reduced or temporarily discontinued until blood pressure is decreased. If these measures fail to lower the blood pressure, a short acting alpha adrenoceptor blocking medicine (e.g. phentolamine, 5 to 60 mg i.v. over 10 – 30 minutes, repeated as necessary) may be administered.

Reflex bradycardia may be expected with a significant increase in blood pressure.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacological classification: 6.1 Cardiac stimulants

Pharmacotherapeutic group: Cardiac stimulants, excluding cardiac glycosides

ATC code: C01C A06

Mechanism of action

Phenylephrine acts predominantly by direct stimulation of alpha1-adrenergic receptors. In therapeutic doses, it has no substantial stimulant effect on the beta-adrenergic receptors of the heart (beta1-adrenergic receptors), but substantial activation of these receptors may occur when larger doses are given. Phenylephrine does not stimulate beta-adrenergic receptors of the bronchi or peripheral blood vessels (beta2-adrenergic receptors). It is believed that alpha1-adrenergic effects result from the inhibition of the production of cyclic adenosine-3',5'-monophosphate (cAMP) by inhibition of the enzyme adenyl cyclase, whereas beta-adrenergic effects result from stimulation of adenyl cyclase activity. Phenylephrine also has an indirect effect by releasing norepinephrine from its storage sites.

Pharmacodynamic effects

The predominant actions of phenylephrine are on the cardiovascular system. Parenteral administration causes a rise in systolic and diastolic pressures. Accompanying the pressor response to phenylephrine is a marked reflex bradycardia that can be blocked by atropine; after atropine, large doses of the medicine increase the heart rate only slightly. Cardiac output is slightly decreased and peripheral resistance is considerably increased. Circulation time is slightly prolonged, and venous pressure is slightly increased; venous constriction is not marked. Most vascular beds are constricted; renal splanchnic, cutaneous and limb blood flows are reduced but coronary blood flow is increased. Pulmonary vessels are constricted, and pulmonary arterial pressure is raised.

Clinical efficacy and safety

Phenylephrine is a potent vasoconstrictor that acts almost exclusively through stimulation of alpha 1-adrenergic receptors. Such arterial vasoconstriction, also accompanied by venous vasoconstriction, provides an increase in blood pressure and bradycardia reflex and its pressor activity is weaker than that of noradrenaline but of longer duration. It is used parenterally in the treatment of hypotensive states, such as those encountered during circulatory failure, general or spinal anaesthesia or medicine induced hypotension. In many published clinical studies phenylephrine was used in low risk pregnant women undergoing spinal anaesthesia during Caesarean delivery.

Phenylephrine allowed to maintain maternal blood pressure near to baseline reduced the incidence of nausea and vomiting without causing foetal acidosis. Actually in therapeutic doses, it produces little if any stimulation of either the spinal cord or cerebrum. A singular advantage of this medicine is the fact that repeated injections produce comparable effects. The potent arterial vasoconstriction resulting in an increase in the resistance of ventricular ejection fraction (increased afterload). Which results in a reduction of cardiac output, this is less pronounced in healthy people but can be exacerbated in the case of previous heart failure.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

After intravenous (IV) administration, a pressor effect occurs almost immediately and persists for 15 – 20 minutes. After intramuscular (IM) administration, a pressor effect occurs within 10 – 15 minutes and persists for 30 minutes to 1 or 2 hours.

Distribution

Phenylephrine undergoes rapid distribution into peripheral tissues; there is some evidence that it may be stored in certain organ compartments. Plasma protein binding is unknown. The volume of distribution is 340 litres, after a single dose, exceeded the body volume by a factor of 5, suggesting a high distribution into certain organ compartments. The pharmacologic effects of phenylephrine are terminated at least partially by uptake into tissues. Penetration of phenylephrine into the central nervous system (CNS) appears to be minimal. Phenylephrine does not appear to be distributed to any great extent into breast milk. The average total serum clearance (2095 ml/min) was close to one-third of the cardiac output.

Biotransformation

Phenylephrine undergoes extensive metabolism in the intestinal wall and in the liver, with only 12 % of the dose excreted unchanged in the urine. The principal routes of metabolism involve sulphate conjugation (primarily in the intestinal wall) and oxidative deamination by monoamine oxidase (MAO) resulting in the formation of the major metabolite (m-hydroxymandelic acid) which accounts for 57 % of the total administered dose; glucuronidation also occurs to a lesser extent.

Elimination

The elimination of phenylephrine is primarily urinary and elimination via the renal route seems to be similar between the IV and per oral routes; 86 % and 80 % of the administered dose, respectively. The

short duration of action of phenylephrine (about 20 minutes after IV injection) suggests a rapid distribution, metabolism and elimination from the body.

Pharmacokinetics in Special Populations

There are no data available on the pharmacokinetics in special populations.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium chloride

Sodium citrate

Citric acid monohydrate

Sodium metabisulphite

Hydrochloric acid, concentrated (for pH adjustment)

Sodium hydroxide (for pH adjustment)

Water for injection

6.2 INCOMPATIBILITIES

PHENYLCORD must not be mixed with other medicines or diluents except those mentioned in section 6.6.

6.3 SHELF LIFE

2 years

After dilution, chemical and physical in-use stability has been demonstrated for 4 hours at room temperature (25 °C).

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to the use are the responsibility of the user and would not

normally be longer than 24 hours at 2° to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at or below 25 °C.

Keep the vial in the outer carton to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

PHENYLCORD solution for injection is packed in a 2 ml siliconised glass vial (type I), with a 13 mm bromobutyl RTS rubber stopper and 13 mm aluminium royal blue flip off seal.

Pack size: 2 ml vials supplied in pack size of 1 vial, 10 vials or 25 vials per pack. Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

PHENYLCORD must be diluted prior to bolus intravenous injection or intravenous infusion.

Bolus intravenous injection:

1 ml of PHENYLCORD 10 mg/ml can be diluted to 200 ml of glucose 5 % injection or sodium chloride 0,9 % injection.

Intravenous infusion:

1 ml of PHENYLCORD 10 mg/ml can be diluted in 500 ml of glucose 5 % solution or sodium chloride 0,9 % solution.

For single use only.

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

requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Accord Healthcare (Pty) Ltd

Building 31, Ground Floor,

Woodlands Office Park,

20 Woodlands Drive, Woodmead,

Johannesburg, 2191

Tel: +27 11 234 5701/2

Email: medinfo@accordhealth.co.za

8. REGISTRATION NUMBER(S)

To be confirmed.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be confirmed.

10. DATE OF REVISION OF THE TEXT