SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINALPRODUCT

Nocof® Drops

2. QUALITATIVE AND QUANTITATIVECOMPOSITION

Each 1ml contains:

Pseudoephedrine Hcl	9.38mg
Chlorpheniramine maleate	1.00mg
Dextromethorphan HBr	3.12mg

{For a full list of excipients, see section 6.1}

3. PHARMACEUTICAL FORM

Drops

A pink liquid with a characteristic bitter and minty odour.

4. Clinical particulars

4.1 Therapeutic indications

Nocof® Drops is indicated in the relief of cough and cold symptoms including running nose and catarrh.

Posology

Up to 3 months: 0.4ml every 4 – 6 hours
3-11 months: 1.0ml (1 dropperful) every 4 – 6 hours

Method of administration

For oral administration.

4.2 Contraindications

Patients with hypersensitivity or idiosyncrasy to any of its ingredients. Sympathomimetic amines are contraindicated in patients with severe hypertension, severe coronary artery disease and patients on monoamine oxidase (MAO) inhibitor therapy. Antihistamines are contraindicated in patients with narrow angle glaucoma, urinary retention, peptic ulcer and during an asthma attack. Dextromethorphan should not be used in patients receiving a monoamine oxidase inhibitor (MAOI) or for 2 weeks after stopping the MAOI drug.

4.3 Special warnings and precautions for use

Dextromethorphan

Should be used with caution in patients with liver disease.

Should be used with caution in atopic children due to histamine release.

Do not take with any other cough and cold medicines.

Use of dextromethorphan with alcohol or other CNS depressants may increase the effects on the CNS and cause toxicity in relatively smaller doses.

Drug dependence, tolerance and potential for abuse

For all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).

Drug withdrawal syndrome

The drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

Serotonin Syndrome

Serotonergic effects, including the development of a potentially life-threatening serotonin syndrome, have been reported for dextromethorphan with concomitant administration of serotonergic agents, such as selective serotonin re-uptake inhibitors (SSRIs), drugs which impair metabolism of serotonin (including monoamine oxidase inhibitors (MAOIs)) and CYP2D6 inhibitors.

Serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, treatment with Almus Dry Cough Linctus with Decongestant Boots Dry Cough & Congestion Relief Oral Solution should be discontinued.

Dextromethorphan is metabolised by hepatic cytochrome P450 2D6. The activity of this enzyme is genetically determined. About 10% of the general population are poor metabolisers of CYP2D6. Poor metabolisers and patients with concomitant use of CYP2D6 inhibitors may experience exaggerated and/or prolonged effects of dextromethorphan. Caution should therefore be exercised in patients who are slow metabolisers of CYP2D6 or use CYP2D6 inhibitors .

Pseudoephedrine

Severe Skin reactions

Severe skin reactions such as acute generalized exanthematous pustulosis (AGEP) may occur with pseudoephedrine-containing products. This acute pustular eruption may occur within the first 2 days of treatment, with fever, and numerous, small, mostly non-follicular pustules arising on a widespread

oedematous erythema and mainly localized on the skin folds, trunk, and upper extremities. Patients should be carefully monitored. If signs and symptoms such as pyrexia, erythema, or many small pustules are observed, administration of Almus Dry Cough Linctus with Decongestant /

Boots Dry Cough & Congestion Relief Oral Solution should be discontinued and appropriate measures taken if needed.

If any of the following occur, this medicine should be stopped

Hallucinations

Restlessness

Sleep disturbances

Caution in moderate to severe renal impairment.

If symptoms persist consult your doctor.

Paediatric population

Serious adverse events may occur in children in case of overdose including neurological disorders. Caregivers should be advised not to exceed the recommended dose.

Chlorpheniramine

Chlorpheniramine, in common with other drugs having anticholinergic effects, should be used with caution in epilepsy; raised intra-ocular pressure including glaucoma; prostatic hypertrophy; severe hypertension or cardiovascular disease; bronchitis, bronchiectasis and asthma; hepatic impairment; renal impairment. Children and the elderly are more likely to experience the neurological anticholinergic effects and paradoxical excitation (eg. Increased energy, restlessness, nervousness). Avoid use in elderly patients with confusion.

The anticholinergic properties of chlorphenamine may cause drowsiness, dizziness, blurred vision and psychomotor impairment in some patients which may seriously affect ability to drive and use machinery.

The effects of alcohol may be increased and therefore concurrent use should be avoided.

Should not be used with other antihistamine containing products, including antihistamine containing cough and cold medicines.

4.4 Interaction with other medicinal products and other forms of interaction

Dextromethorphan

Not to be used in patients taking monoamine oxidase inhibitors or within 14 days of stopping treatment as there is a risk of serotonin syndrome (pyrexia, hypertension, arrhythmias) when MAOIs are taken in combination with dextromethorphan.

Dextromethorphan might exhibit additive CNS depressant effects when co-administered with alcohol, antihistamines, psychotropics, and other CNS depressant drugs.

CYP2D6 inhibitors

Dextromethorphan is metabolized by CYP2D6 and has an extensive first-pass metabolism. Concomitant use of potent CYP2D6 enzyme inhibitors can increase the dextromethorphan concentrations in the body to levels multifold higher than normal. This increases the patient's risk for toxic effects of dextromethorphan (agitation, confusion, tremor, insomnia, diarrhoea and respiratory depression) and development of serotonin syndrome. Potent CYP2D6 enzyme inhibitors include fluoxetine, paroxetine, quinidine and terbinafine. In concomitant use with quinidine, plasma concentrations of dextromethorphan have increased up to 20-fold, which has increased the CNS adverse effects of the agent. Amiodarone, flecaninde and propafenone, sertraline, bupropion, methadone, cinacalcet, haloperidol, perphenazine and thioridazine also have similar effects on the metabolism of dextromethorphan. If concomitant use of CYP2D6 inhibitors and dextromethorphan is necessary, the patient should be monitored and the dextromethorphan dose may need to be reduced.

Pseudoephedrine

MAOIs and/or RIMAs: should not be given to patients treated with MAOIs or within 14 days of stopping treatment: increased risk of hypertensive crisis.

Moclobemide: risk of hypertensive crisis.

Antihypertensives (including adrenergic neurone blockers & beta-blockers): this medicine may block the hypotensive effects.

Cardiac glycosides: increased risk of dysrhythmias.

Ergot alkaloids (ergotamine & methysergide): increased risk of ergotism.

Appetite suppressants and amphetamine-like psychostimulants: risk of hypertension.

Oxytocin – risk of hypertension.

Enhances the effects of **anticholinergic drugs** (such as TCAs).

There is an increased risk of arrhythmias if given to patients receiving anticholinergic drugs such as tricyclic antidepressants.

Concomitant use with sympathomimetic agents such as decongestants, tricyclic antidepressants, may occasionally cause a rise in blood pressure.

Chlorpheniramine

Chlorpheniramine may enhance the sedative effects of CNS depressants, including alcohol, barbiturates, hypnotics, anxiolytics, sedatives and anti-psychotics. As chlorpheniramine possesses anticholinergic activity the effects of some anticholinergics may be potentiated.

4.5 Pregnancy and Lactation

Pregnancy

There are limited amount of data on the use of pseudoephedrine in pregnant women. The use of pseudoephedrine during the first trimester of pregnancy has been associated with an increased frequency of gastroschisis (a developmental defect in the abdominal wall with intestinal herniation) and of small intestinal atresia (congenital obstruction of small intestine). Due to the vasoconstrictive properties of pseudoephedrine, it may induce a reduction in uteroplacental circulation.

Pseudoephedrine is not recommended in pregnancy.

Breast-feeding

Pseudoephedrine has been detected in human milk with a small percentage of the maternal dose potentially administered to the breastfed infant. Irritability and disturbed sleep have been reported in breastfed infants. Pseudoephedrine may supress lactation.

Dextromethorphan

There is no data on the secretion of dextromethorphan into breast milk and therefore use of this product during lactation should be avoided.

Chlorpheniramine

Pregnancy

There are no adequate data from the use of chlorphenamine in pregnant women. The potential risk for humans is unknown, Use during the third trimester may result in reactions in the newborn or premature neonates. Not to be used during pregnancy unless considered essential by a physician.

Lactation

Chlorphenamine maleate and other antihistamines may inhibit lactation and may be secreted in breast milk. Not to be used during lactation unless considered essential by a physician.

4.6 Effects on ability to drive and use machines

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 a '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

4.7 Undesirable effects

Cough syrups are normally tolerated at therapeutic doses. In large doses, side effects such as headache, drowsiness, dizziness, gastro-intestinal disturbances such as nausea, vomiting, diarrhea or constipation may be observed. Others include difficulty in micturition, muscular weakness and tremor, anxiety, restlessness, excitation and mental confusion.

Very high doses may produce respiratory depression.

4.8 Overdose

Symptoms: Should antihistamine effects predominate, central action constitutes the greatest danger. In the small child, predominant symptoms are excitation, hallucination, ataxia, incoordination, tremors, flushed face and fever. Convulsions, fixed and dilated pupils, coma and death may occur in severe cases. In the adult, fever and flushing are uncommon; excitement leading to convulsions and postictal depression is often preceded by drowsiness and coma. Respiration is usually not seriously depressed; blood pressure is usually stable.

Should sympathomimetic symptoms predominate; central effects include restlessness, dizziness, tremor, hyperactive reflexes, talkativeness, irritability and insomnia. Cardiovascular and renal effects include difficulty in micturition, headache, flushing, palpitation, cardiac arrhythmia, hypertension with subsequent hypotension and circulatory collapse. Gastrointestinal effects include dry mouth, metallic taste, anorexia, nausea, vomiting, diarrhea and abdominal cramps.

Dextromethorphan may cause respiratory depression with a large overdose

Management of over dosage involves supportive and symptomatic therapy. In severe over dosage empty the stomach by aspiration and gastric lavage.Patients should be kept quiet to minimize the excitation which occurs particularly in children. Diazepam may be given to control CNS stimulation and convulsion.

Overdosage with antihistamines may cause hallucinations, convulsions or possibly death, especially in infants and children. Antihistamines are more likely to cause dizziness, sedation, and hypotension in elderly patients. Overdosage with sympathomimetic amines can cause cardiac arrhythmias, cerebral hemorrhage and pulmonary edema. It can also cause palpitations, tremor, dizziness, vomiting, fear, labored breathing, headache, pallor, weakness, hallucinations, and delirium.

• If the amount ingested is considered dangerous or excessive induce vomiting with ipecac syrup unless the patient is convulsing, comatose, or has lost the gag reflex, in which case perform gastric lavage.
• Gastric lavage (isotonic or 0.45% sodium chloride solution) if patient is unable to vomit within 3 hours of ingestion.
• Saline cathartics (milk of magnesia) are sometimes used.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pseudoephedrine is a sympathomimetic agent with direct and indirect effects on adrenergic receptors. It has alpha and beta adrenergic activity and some stimulant effect on the central nervous system. The sympathomimetic effect of pseudoephedrine produces vasoconstriction which in turn relieves nasal congestion.

Dextromethorphan is a cough suppressant.

Chlorpheniramine is one of the most potent anti-histamines. It is useful in the control of symptoms which are allergic in origin. It helps to provide relief from nasal stuffiness and watering of the eyes.

5.2 Pharmacokinetic properties

Pseudoephedrine is readily and completely absorbed from the gastrointestinal tract and is largely excreted in the urine unchanged. It has an elimination half-life of 5 to 8 hours but its urinary elimination and hence half-life is pH dependent. Pseudoephedrine is rapidly distributed throughout the body, its volume of distribution being 2 to 3 L/kg bodyweight.

Dextromethorphan is well absorbed from the gastrointestinal tract, metabolised in the liver and excreted as both unchanged drug and demethylated metabolites.

Dextromethorphan undergoes rapid and extensive first-pass metabolism in the liver after oral administration. Genetically controlled O-demethylation (CYD2D6) is the main determinant of dextromethorphan pharmacokinetics in human volunteers.

It appears that there are distinct phenotypes for this oxidation process resulting in highly variable pharmacokinetics between subjects. Unmetabolised dextromethorphan, together with the three demethylated morphinan metabolites dextrorphan (also known as 3-hydroxy-N-methylmorphinan), 3-hydroxymorphinan and 3-methoxymorphinan have been identified as conjugated products in the urine.

Dextrormethophan, which also has antitussive action, is the main metabolite. In some individuals metabolism proceeds more slowly and unchanged dextromethorphan predominated in the blood and urine.

Chlorpheniramine maleate is readily absorbed from the gastro-intestinal tract. It is extensively metabolised in the liver and excreted in the urine.

6. PHARMACEUTICALPARTICULARS

6.1 List of excipients

Methyl Paraben
Bronopol
Sorbitol Solution
Sodium Saccharine
Glycerine
Citric Acid
Peppermint Oil
Tutti Fruitti
Flavour
Allura Red Colour
Tartrazine Orange
Colour
Sugar
Sodium Citrate

6.2 Incompatibilities

None known

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store between 30°C and away from the reach of children.

6.5 Nature and contents of container

Amber Glass bottle of 15ml and 30ml with cap and measuring device

6.6 Special precautions for disposal

No special requirements

7 APPLICANT/MANUFACTURER

Afrab-Chem Limited,

22, Abimbola Street,
Isolo Ind. Estate,
Isolo, Lagos.
Nigeria.