1. NAME OF THE MEDICINAL PRODUCT
Avrocold Tablet

2. Qualitative and quantitative composition
Each tablet contains:

Paracetamol 500mg

Phenylephrine Hydrochloride 5mg

Chlorpheniramine Maleate 2mg

For full list of excipients, see section 6.1

3. Pharmaceutical form
Solid (Oral Tablet).

4. Clinical particulars
4.1 Therapeutic indications
Avrocold tablet is indicated for the relief of cold and influenza and its accompanying symptoms including fever, headache, sore throat pain, catarrh nasal congestion, sinusitis and body aches and pains.

4.2 Posology and method of administration
Adults and children 12 years and over

Two tablets. Repeat every six hours. Do not take more than 8 tablets in 24 hours.

Do not exceed the stated dose.

Minimum dosing interval: 4 hours.

The lowest dose necessary to achieve efficacy should be used for the shortest duration of treatment.

Not to be given to children under 12 years except on medical advice.

Elderly

The normal adult dose may be taken.

Do not take continuously for more than 5 days without medical advice.

Method of administration: Oral

4.3 Contraindications
- The product is contra-indicated in patients who are hypersensitive to any of the components of the preparation and in neonates and premature infants owing to their increased susceptibility to the antimuscarinic effect of anti-histamines. It is also contra-indicated in patients with hepatic or renal impairment and in acute attacks of asthma.

- It is contraindicated in patients with severe hyperthyroidism and in severe ischaemic heart disease due to the risk of tachycardia or reflex bradycardia.

- It is contraindicated in chronic alcoholics or patients on sedatives since it potentiates the drowsiness effect.
- Concomitant use of other sympathomimetic decongestants.
- Phaeochromocytoma.
- Closed angle glaucoma.
- An enlargement of the prostate gland
- Hepatic or severe renal impairment, hypertension, hyperthyroidism, diabetes, heart disease or those taking tricyclic antidepressants or beta-blocking drugs and those patients who are taking or have taken, within the last two weeks, monoamine oxidase inhibitors (see section 4.5).

4.4 Special warnings and precautions for use
May cause drowsiness, if affected do not drive or operate machinery.

Contains paracetamol. Do not take with any other paracetamol-containing products. The concomitant use with other products containing paracetamol may lead to an overdose. Paracetamol overdose may cause liver failure which may require liver transplant or lead to death.

Avoid alcoholic drinks

Concomitant use of decongestants and other cough and cold medicines should be avoided.

Consult your doctor before using the product if you are taking other prescription medicines including monoamine oxidase inhibitors (MAOI) or antihypertensives and if you are pregnant or breast feeding.

Use with caution in patients taking the following medications (see Interactions)

This product should not be used by patients taking other sympathomimetics (such as decongestants, appetite suppressants and amphetamine-like psychostimulants)

Keep out of the sight and reach of children.

4.5 Interaction with other medicinal products and other forms of interaction
Paracetamol
Anticholinergic agents or opoid analgesics delay the gastrointestinal absorption of paracetamol by decreasing gastric emptying. Repeated doses of paracetamol increase the anticoagulant response to coumarins.
Paracetamol increases chloramphenicol concentrations and toxicity may be increased by the concomitant use of enzyme-inducing agents such as alcohol or anti-epileptic drugs. Paracetamol increases the blood concentrations of unhydrolysed aspirin.

The absorption of Paracetamol may be accelerated by drugs such as Metoclopramide. Excretion may be affected and plasma concentrations altered when given with Probenecid. Colestyramine reduces the absorption of Paracetamol if given within 1hour of Paracetamol.

Chlorpheniramine
Chlorpheniramine may enhance the sedating effects of CNS depressants including alcohol, barbiturates, hypnotics, opoid analgesics, anxiolytic sedatives and psychotics. It is incompatible with calcium chloride, kanamycin sulphate, noradrenaline tartrate and meglumine adiopone.
It has additive antimuscarinic action with other antimuscarinic drugs like atropine, tricyclic antidepressants, and MAOIs.
It has been suggested that sedating antihistamines could mask the warning signs of damage caused by ototoxic drugs such as aminoglycoside antibiotics.
Chlorpheniramine may suppress cutaneous histamine response to allergen extracts. Its therapy should be stopped several days before skin testing.

Phenylephrine
Hazardous arrhythmias are a risk if phenylephrine is used in patients anaesthesised with cyclopropane, halothane or other volatile anaesthetics that sensitise the myocardium to its adrenergic effects.
The vasoconstrictor and pressor effects of phenylephrine may be enhanced by drugs with similar effects such as ergot alkaloids or oxytocin.

Phenylephrine reverses the antihypertensive effects of adrenergic blockers such as guanethidine and reserpine with the risk of severe hypertension.

The action of phenylephrine may be enhanced by MAOI and tricyclic antidepressants resulting in hazardous hypertensive effects.
The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding. The hepato-toxicity of paracetamol may be potentiated by excessive intake of alcohol. The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by colestyramine. Pharmacological interactions involving

paracetamol with a number of other drugs have been reported. These are considered to be of unlikely clinical significance in acute use at the dosage regimen proposed.

Phenylephrine should be used with caution in combination with the following drugs as interactions have been reported:

Monoamine oxidase inhibitors (including moclobemide)	Hypertensive interactions occur between sympathomimetic amines such as phenylephrine and monoamine oxidase inhibitors (see contraindications)..
Sympathomimetic amines	Concomitant use of phenylephrine with other sympathomimetic amines can increase the risk of cardiovascular side effects.
Beta-blockers and other antihypertensives (including debrisoquine, guanethidine, reserpine, methyldopa)	Phenylephrine may reduce the efficacy of beta-blocking drugs and antihypertensive drugs. The risk of hypertension and other cardiovascular side effects may be increased.
Tricyclic antidepressants (e.g. amitriptyline)	May increase the risk of cardiovascular side effects with phenylephrine.
Ergot alkaloids (ergotamine and methylsergide)	Increased risk of ergotism
Digoxin and cardiac glycosides	Increase the risk of irregular heartbeat or heart attack
Warfarin and other coumarins	The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

If urine is collected within 24 hours of a dose of this product, a metabolite may cause a colour interference with laboratory determinations of 5 hydroxyindoleacetic acid (5-HIAA) and vanillymandelic acid (VMA).

4.6 Pregnancy and lactation

This product should not be used during pregnancy without medical advice. Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosage, but patients should follow the advice of their doctor regarding its use. The safety of phenylephrine during pregnancy has not been established.

Paracetamol and phenylephrine are excreted in breast milk but not in a clinically significant amount. This product should not be used in breast feeding without medical advice.

4.7 Effects on ability to drive and use machines

Patients should be advised not to drive or operate machinery if affected by dizziness.

4.8 Undesirable effects

Adverse events from historical clinical trial data are both infrequent and from small patient exposure. Events Side effects are rare and usually mild. The most reported being gastrointestinal disturbances like loss of appetite, nausea, vomiting, epigastric pain, constipation or diarrhoea and their incidence might be reduced by giving the drug with meals.

Also reported are headache, sedation, psychomotor impairment, antimuscarinic effects like dry mouth, thickened respiratory tract secretions, urinary retention or frequency, dysuria, increased gastric reflux and CNS depression including dizziness, lassitude, blurred vision and incordination, which may diminish after few days of treatment. Hypersensitivity reactions and rashes may also occur.

Concurrent ingestion of alcohol or other CNS depressants produce an additive effect that impairs motor skills. If the product is taken within the recommended dose side effects do not usually present.

4.9 Overdose

Paracetamol

Liver damage is possible in adults who have taken 10g or more of paracetamol. Ingestion of 5g or more of paracetamol may lead to liver damage if the patient has risk factors (see below).

Risk factors: If the patient a, Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes. Or

b, Regularly consumes ethanol in excess of recommended amounts. Or

c, Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms:

Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Management:
Immediate treatment is essential in the management of paracetamol overdose, even if symptoms of overdose are not present. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines, see BNF overdose section.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable). Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol, however, the maximum protective effect is obtained up to 8 hours post-ingestion. The effectiveness of the antidote declines sharply after this time. If required the patient should be given intravenous N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital. Management of patients who present with serious hepatic dysfunction beyond 24h from ingestion should be discussed with the NPIS or a liver unit.

Phenylephrine

Symptoms and signs
Phenylephrine overdosage is likely to result in effects similar to those listed under adverse reactions. Additional symptoms may include hypertension and possibly reflux bradycardia. In severe cases confusion, hallucinations, seizures and arrhythmias may occur. However the amount required to produce serious phenylephrine toxicity would be greater than required to cause paracetamolrelated toxicity.

Treatment
Treatment should be as clinically appropriate. Severe hypertension may need to be treated with an alpha blocking drug such as phentolamine.

Chlorpheniramine

Symptoms and signs
Very large doses of Chlorpheniramine cause restless, nausea and vomiting.

Treatment
Vomiting would be treated by fluid replacement and monitoring of electrolytes if indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATCCode: N02BE 51 Paracetamol combinations excluding psycholeptics.

Paracetamol is an analgesic and antipyretic.
Chlorpheniramine is an antihistamine.
Phenylephrine Hydrochloride is a sympathomimetic decongestant.
The active ingredients are known to cause sedation.

Paracetamol:
Paracetamol a Para – aminophenol derivative has antipyretic and analgesic properties but has no anti-inflammatory properties. Paracetamol acts by its selective depressant action on pain perception apparatus of the thalamus and hypothalamus in the CNS.
Paracetamol reduces fever by a direct effect on the heat regulating centres of the CNS, increasing dissipation of body heat by increasing peripheral blood flow and perspiration.

Phenylephrine Hydrochloride
Phenylephrine Hydrochloride is a symphatomimetic with mainly direct effects on adrenergic receptors. It has predominantly alpha-adrenergic activity and is without significant stimulating effects on central nervous system at usual doses. It activates beta-adrenergic receptors only at much higher concentrations. Its pressor activity is weaker than that of noradrenaline but of longer duration.
It is used as a nasal decongestant. It acts by decreasing resistance to airflow by decreasing the volume of the nasal mucosa. This may occur by activation of alpha adrenergic receptors in venous capacitance vessels in nasal tissues that have erectile characteristics.
It reduces intestinal tone and motility, causes bronchodilatation and relaxes the bladder wall. It has stimulant activity on the respiratory centre.

Chlorpheniramine:
Chlorpheniramine is an akylamine derivative with the actions and uses of the antihistamines. It has significant sedative properties. It also has anti-muscarinic properties.
Chlorpheniramine diminishes or abolishes the main actions of histamine in the body by competitive, reversible blockade of histamine receptor sites on the tissues. It does not inactivate or prevent the release or synthesis of histamine.
Chlorpheniramine is often used in combination preparations for the treatment of coughs and colds. The mechanism of its antitussive action may involve reduction in cholinergic nerve transmission or may simply result from its sedative effects.

5.2 Pharmacokinetic properties

Paracetamol:
Paracetamol is readily absorbed from the gastrointestinal tract with peak plasma concentration occurring about 30 minutes to 2 hours after ingestion. It is distributed into most body tissues and metabolised in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted as unchanged Paracetamol. The elimination half lives varies from 1 to 4 hours. Plasma protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

A minor hydroxylated metabolite (N – acetyl – P – benzoquinoneimine) which is usually produced in very small amounts by mixed-function oxidases in the liver, and which is usually detoxified by conjugation with liver glutathione may accumulate following paracetamol over-dosage and cause liver damage.

Phenylephrine Hydrochloride
Phenylephrine Hydrochloride is absorbed from the gastrointestinal tract and has low oral bioavailability owing to irregular absorption and first-pass effect metabolism by monoamine oxidase in the gut and liver. It has been shown to accumulate to toxic concentrations in children with renal tubular acidosis.

Chorpheniramine Maleate:
Chlorpheniramine is absorbed slowly from the GIT, peak plasma concentration occurring about 2.5 to 6 hours after administration. Chlorpheniramine appears to undergo considerable first-pass metabolism. About 70% of chlorpheniramine in the circulation is bound to plasma proteins.
There is wide inter-individual variation in the pharmacokinetics of chlorpheniramine; values ranging from 2 to 43 hours have been reported for the half-life. Chlorpheniramine is widely distributed in the body and enters the CNS.
Chlorpheniramine is extensively metabolised. Metabolites include desmethyl- and didesmethyl-chlorpheniramine. Unchanged drug and metabolites are excreted primarily in the urine; excretion is dependent on urinary PH and flow rate. Only trace amounts have been found in the faeces.
More rapid and extensive absorption, faster clearance and a shorter half-life have been reported in children.

5.3 Preclinical safety data
Preclinical safety data on these active ingredients in the literature have not revealed any pertinent and conclusive findings which are of relevance to the recommended dosage and use of the product and which have not already been mentioned elsewhere in this SPC.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Methyl Hydroxybenzoate
Maize Starch
Povidone K.30
Talc
Magnesium Stearate
Aerosil

6.2 Incompatibilities
None known.

6.3 Shelf life
Three years.

6.4 Special precautions for storage
Store below 30^{o}C. Protect form light

6.5 Nature and contents of container
Avrocold Tablet is packed in an Alu-Alu strip foil

Pack size: 4 x 25 tablets

6.6 Special precautions for disposal and other handling
Not applicable.

7. Applicant/manufacturer
Avro Pharma Limited
Daid House Plot 2, Block J, Limca Way,
Isolo Industrial Estate, Oshodi-Apapa Expressway,
Isolo, Lagos State, Nigeria.
Tel: +234(1)2913955
Email: avro@rumon-org.com