1.3. PRODUCT INFORMATION

1.3.1 Summary of Product Characteristics (SmPC)

National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

1. NAME OF THE MEDICINAL PRODUCT

SUDREX COLD & COUGH, double-layer caplet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each caplet contains:

Paracetamol	500 mg
Caffeine	30 mg
Phenylephrine HCl	10 mg
Dextromethorphan HBr	12 mg

Excipients with known effect:

- FD&C Yellow No. 5 (Tartrazine)
- FD&C Yellow No. 6 (Sunset Yellow)
- Glycerol

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Caplet

Double-layer caplet, red color on one side and yellow color on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

To relieve symptoms of cold such as headache, fever, nasal, decongestion, sneezes and cough without sputum.

4.2 Posology and method of administration

Adults: 1 caplet 3 - 4 times daily.

Elderly : As for adults

Children : not recommended for children under 12 years of age.

For oral administration only.

4.3 Contraindications

See box warning

Patients with severe liver disorder.

Patiets with hypersensitivity to any of the ingredients.

4.4 Special warnings and precautions for use

- It should not be given to people who are sensitive to other sympathomimetic drugs (eg. Ephedrine, phenylpropanolamine, pseudoephedrine), severe high blood pressure patients who received drug therapy and anti-depressant type monoamine oxidase inhibitors (MAO).
- May not exceed the recommended dose.
- Careful use in patients with high blood pressure who have potential or high blood pressure ore stroke, such as in patients with excess weight (over weight) or elderly patients.
- If within 3 days the symptoms are not reduced immediately, contact your doctor or health care units.
- Stop using this medication in case of insomnia, palpitations and dizziness.

- Caution patients with hepatic and renal impairment, glaucoma, prostatic hypertrophy, hyperthyroidism, heart failure and diabetes mellitus.
- Not recommended for children under 12 years of age, pregnancy and lactation woman except with doctor's instruction.
- Co-administration with alcohol may increase risk damage of liver function. The hazard of overdose is greater in those with non-cirrhotic alcoholic liver disease. Underlying liver disease increases the risk of paracetamol-related liver damage.
- Patients should be advised not to take other paracetamol-containing products concurrently. 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. Concomitant use of other decongestants or cold and flu medicines should be avoided.
- Patients suffering from chronic cough as occurs with smoking, asthma or patients suffering from an acute asthma attack, or where cough is accompanied by excessive secretions should be advised to consult a Healthcare Professional before use.
- Causes of chronic cough should be excluded if symptoms are persistent. Any accompanying symptoms should be actively sought and appropriately investigated/ treated. Stop use and ask your healthcare professional if your cough lasts more than 7 days, comes back or is accompanied by a fever, rash or persistent headache. These could be signs of serious conditions.
- Cases of dextromethorphan abuse have been reported. Caution is particularly recommended for adolescents and young adults as well as in patients with a history of drug abuse or psychoactive substances.
- 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 metabolizers of CYP2D6 or use CYP2D6 inhibitors (see also section 4.5).
- Medical advice should be sought before taking this medicine in patients with: glutathione depletion due to metabolic deficiencies.
- An enlargement of the prostate gland
- Occlusive vascular disease (e.g. Raynaud's phenomenon)
- Cardiovascular disease
- This product should not be used by patients taking other sympathomimetics (such as decongestants, appetite suppressants and amphetamine-like psychostimulants) (see interactions).
- Excessive intake of caffeine (e.g. coffee, tea and some canned drinks) should be avoided while taking this product.
- Do not exceed the recommended dose.
- If symptoms persist consult your doctor.

- Keep out of the sight and reach of children.
- Consult your doctor if you are taking warfarin.
- Contain sunset yellow & tartrazine which may cause an allergic reaction.

4.5 Interaction with other medicinal products and other forms of interaction

Enzyme-inducing drugs may increase hepatic damage, as does excessive intake of alcohol. The speed of absorption of paracetamol may be increased by metoclopromide or domperidone and absorption reduced by colestyramine. These interactions are considered to be of unlikely clinical significance in acute use at the dosage regimen proposed.

Do not use if you are now taking a prescription monoamine oxidase inhibitor (MAOI), a selective serotonin reuptake inhibitor (SSRI), or other medications for depression, psychiatric, or emotional conditions, or Parkinson's disease, or for 2 weeks after stopping the medication. If you are not sure if your prescription medication contains one of these drugs, ask a doctor or pharmacist before taking this product.

Medical advice should be sought before taking paracetamol-caffeine phenylephrine dextromethorphan in combination with the following drugs:

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 sympathomimetics amines can increase the risk of cardiovascular side effects (see warnings and precautions).
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 (see contraindications).
Tricyclic antidepressants (e.g. amitriptyline)	May increase the risk of cardiovascular side effects with phenylephrine (see contraindications).
Digoxin and cardiac glycosides	Concomitant use of phenylephrine with digoxin or cardiac glycosides may increase the risk of irregular heartbeat or heart attack.
Ergot alkaloids (e.g. ergotamine and methylsergide)	Concomitant use of phenylephrine hydrochloride may cause an increased risk of ergotism *(see Warnings and Precautions).*
Warfarin and other coumarins	The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of paracetamol with an increased risk of bleeding; occasional doses have no significant effect.
Lithium	Caffeine can increase the elimination of lithium from the body. If taken concomitantly, it is recommended to reduce or moderate the intake of caffeine.
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, flecainide and propafenone, sertraline, bupropion, methadone, cinacalcet, haloperidol, perphenazine andthioridazine 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.

4.6 Pregnancy and Lactation

Pregnancy

This product is not recommended for use in pregnancy due to the phenylephrine and caffeine content. There is a potential increased risk of lower birth weight and spontaneous abortion associated with caffeine consumption during pregnancy. Pregnant women should seek medical advice before taking paracetamol.

Breast-feeding

This product should not be used while breast-feeding without medical advice. Avoid the use of the product during lactation, unless the benefits to the mother outweigh the risks to the infant. If used, the lowest effective dose and shortest duration of treatment should be considered.

Paracetamol is excreted in breast milk but not in a clinically significant amount at recommended dosages. Caffeine in breast milk may have a stimulating effect on breast-fed infants but significant toxicity has not been observed. Phenylephrine may be excreted in breast milk. It is not known whether dextromethorphan or its metabolites are excreted in human milk.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

Patients should be advised not to drive or operate machinery if affected by dizziness and drowsiness. This medicine can impair cognitive function and can affect a patient's ability to drive safely.

4.8 Undesirable effects

Psychomotor disturbances, tachycardia, arrhythmia, palpitations, and urinary retention, drowsiness (rarely). High dose and in prolonged therapy cause hepatic impairment.

Adverse events from historical clinical trial data are both infrequent and from small patient exposure. Accordingly, events reported from extensive post-marketing experience at therapeutic/labelled dose and considered attributable are tabulated below by system class. Due to limited clinical trial data, the frequency of these adverse events is not known (cannot be estimated from available data), but post-marketing experience indicates that adverse reactions to paracetamol are rare and serious reactions are very rare.

Paracetamol

Body System	Undesirable effect
Blood and lymphatic system disorders	Thrombocytopenia Agranulocytosis These were not necessarily causally related to paracetamol.
Immune system disorders	Anaphylaxis Cutaneous hypersensitivity reactions including skin rashes, angiodema Very rare cases of serious skin reactions have been reported.
Respiratory, thoracic and mediastinal disorders	Bronchospasm*
Hepatobiliary disorders	Hepatic dysfunction

* There have been cases of bronchospasm with paracetamol, but these are more likely in asthmatics sensitive to aspirin or other NSAIDs.

Caffeine

Adverse reactions identified through post-marketing use with caffeine are listed below. The frequency of these reactions is unknown.

Body System	Undesirable effect
Central Nervous system	excitability, dizziness and headache
Psychiatric disorders	Nervousness, insomnia, restlessness, anxiety and irritability
Cardiac disorders	Palpitations
Gastrointestinal disorders	Gastrointestinal disturbances

When the recommended paracetamol-caffeine dosing regimen is combined with dietary caffeine intake, the resulting higher dose of caffeine may increase the potential for caffeine-related adverse effects.

Phenylephrine

The following adverse events have been observed in clinical trials with phenylephrine and may therefore represent the most commonly occurring adverse events.

Body System	Undesirable effect
Psychiatric disorders	Nervousness
Nervous system disorders	Headache, dizziness, insomnia
Cardiac disorders	Increased blood pressure
Gastrointestinal disorders	Nausea, Vomiting

Dextromethorphan

Adverse effects are rare, however the following side effects may be associated with dextromethorphan

hydrobromide:

Body System	Undesirable effect
Gastrointestinal Disorders	Gastrointestinal upset
Nervous System Disorders	Dizziness, drowsiness, mental confusion
Immune System Disorders	Hypersensitivity

Adverse reactions identified during post-marketing use are listed below. The frequency of these reactions is unknown

Body System	Undesirable effect
Immune system disorders	Hypersensitivity, allergic dermatitis, urticaria
Eye disorders	Mydriasis, acute angle closure glaucoma, most likely to occur in those with closed angle glaucoma
Cardiac disorders	Tachycardia, palpitations
Skin and subcutaneous disorders	Rash
Renal and urinary disorders	Dysuria, urinary retention. This is most likely to occur in those with bladder outlet obstruction, such as prostatic hypertrophy.

4.9 Overdose

Paracetamol

Paracetamol overdose may cause liver failure which may require liver transplant or lead to death.

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 and signs

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 and have peaked after 4-6 days. 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.

Treatment

Immediate treatment is essential in the management of paracetamol overdose. 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. Acute pancreatitis has been observed, usually with hepatic dysfunction and liver toxicity.

Caffeine

Symptoms and signs

Overdose of caffeine may result in epigastric pain, vomiting, diurese, tachycardia or cardiac arrhythmia, CNS stimulation (insomnia, restlessness, excitement, agitation, jitteriness, tremors and convulsions).

It must be noted that for clinically significant symptoms of caffeine overdose to occur with this product, the amount ingested would be associated with serious paracetamol-related liver toxicity.

Treatment

No specific antidote is available, but supportive measures such as beta adrenoceptor antagonists to reverse the cardiotoxic effects may be used.

Phenylephrine

Symptoms and signs

Phenylephrine overdosage is likely to result in effects similar to those listed under adverse reactions. Additional symptoms may include, irritability, restlessness, hypertension, and possibly reflex bradycardia. In severe cases confusion, hallucinations, seizures and arrhythmias may occur. However the amount required to produce serious phenylephrine toxicity would be greater than that required to cause paracetamol-related liver toxicity.

Treatment

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

If overdose is confirmed or suspected, seek immediate advice from your Poison Centre and refer patient to nearest Emergency Medical Centre for management and expert treatment. This should happen even in patients without symptoms or signs of overdose due to the risk of delayed liver damage.

Dextromethorphan

Symptoms

These include nausea and vomiting, CNS depression, dizziness, dysarthria (slurred speech), myoclonus, nystagmus, somnolence (drowsiness), tremor, excitation, mental confusion, psychotic disorder (psychosis), and respiratory depression.

Treatment

Treatment of overdose should be symptomatic and supportive. Gastric lavage may be of use. Naloxone has been used successfully as a specific antagonist to dextromethorphan toxicity in children.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Paracetamol is a well established analgesic and antipyretic.

Phenylephrine hydrochloride is a sympathomimetic agent with mainly direct effects on adrenergic receptors (predominantly alpha-adrenergic activity) producing nasal decongestion.

Caffeine is the most active xanthine derivative in respect of stimulation of the central nervous system, producing a condition of wakefulness and increased mental activity.

Dextromethorphan hydrobromide is a cough suppressant which has a central action on the cough centre in the medulla. It has no analgesic properties and little sedative activity.

5.2 Pharmacokinetic properties

Paracetamol is metabolised by the hepatic microsomal enzymes. It is rapidly and completely absorbed from the gastro- intestinal tract. Plasma concentration reaches a peak in half to one hour, the plasma half-life is one to three hours and it is uniformly distributed throughout the body.

Phenylephrine hydrochloride is irregularly absorbed from the gastro-intestinal tract. When injected intramuscularly it takes 10- 15 minutes to act and subcutaneous and intramuscular injections are effective for about one hour. Intravenous injections are effective for about 20 minutes.

Caffeine is readily absorbed from the gastro-intestinal tract.

Dextromethorphan hydrobromide is well absorbed from the gastrointestinal tract. 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. 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. Dextrorphan, which also has antitussive action, is the main metabolite. In some individuals metabolism proceeds more slowly and unchanged dextromethorphan predominates in the blood and urine.

5.3 Preclinical safety data

Not Applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose (Avicel PH-101)
FD&C Red No. 3 (Erythrosine)
FD&C Yellow No. 5 (Tartrazine)
FD&C Yellow No. 6 (Sunset Yellow)
Gelatin
Glycerol
Magnesium stearate
Methyl hydroxybenzoate (Nipagin)
Maize starch
Sodium starch glycolate
Propyl hydroxybenzoate (Nipasol)
Talc

6.2 Incompatibilities

None.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store below 30°C. Keep out of reach and sight of children.

6.5 Nature and contents of container

10 caplets are packed into PVC 250 µm / aluminium foil 20 µm + heat seal coating 6-8 gsm blister in a sleeve of duplex carton 250 gsm. 10 sleeves are packed in an outer duplex carton 310 gsm.

6.6 Special precautions for disposal and other handling

None.

7. APPLICANT/MANUFACTURER

Applicant

Orange Drug Ltd.

66/68 Town Planning Way Ilupeju

Lagos – NIGERIA

Manufacturer

PT. Tempo Scan Pacific

EJIP Industrial Park, Plot 1 G-H, Cikarang, Bekasi 17550 - INDONESIA