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 JOINT & MUSCLE PAIN, double-layer caplet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each caplet contains:

Paracetamol	325 mg
Ibuprofen	200 mg
Caffeine	30 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 orange color on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

To relieve mild to moderate musculoskeletal pain (joint and muscle pain).

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

- Patients with hypersensitivity to Ibuprofen, Paracetamol, Acetosal and other NSAIDs.
- Patients with a history of peptic ulcer.
- Patients with nasal polyps, angioedema and bronchospastic reaction to acetosal.
- In final trimester of pregnancy.

4.4 Special warnings and precautions for use

- Beware of people with bronchospasm, allergic rhinitis and urticaria due to acetosal or other NSAIDs because of the possibility of cross-sensitivity.
- Be careful when used in patients with a history of upper gastrointestinal disease and heart disease, hypertension and conditions associated with fluid retension and intrinsic coagulation disorders.
- Not recommended for use in children aged less than 12 years because the possibility of liver disruption.
- Report to your doctor if the following symptoms appear: stomach bleeding, blurred vision or eye problems, skin rashes, weight gain or edema.
- Not recommended to be use during breast feeding and pregnancy.
- Be careful on the abnormalities of liver function and kidney function and need to be monitored carefully.
- Hypersensitivity reactions may occur and increase in serum transaminase in patients with lupus erythematosus.
- Do not exceed the recommended dose because it may cause liver damage.
- If after 5 days of pain did not disappear, immediately contact your doctor or health care units.

4.5 Interaction with other medicinal products and other forms of interaction

Medical advice should be sought before taking paracetamol, ibuprofen and caffeine in combination with the following drugs:

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.
Acetylsalicylic Acid	Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects, unless low-dose acetylsalicylic acid (not above 75 mg daily) has been advised by a doctor. Experimental data suggest that Ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use
Other NSAIDs	Other NSAIDs including cyclo-oxygenase-2 selective inhibitors as these may increase the risk of adverse effects.
Cholestyramine	The speed of absorption of paracetamol is reduced by cholestyramine. Therefore, cholestyramine should not be taken within one hour if maximal analgesia is required.

Metoclopramide and Domperidone	The absorption of paracetamol is increased by metoclopramide and domperidone. However, concurrent use need not be avoided
Anticoagulants	NSAIDs may enhance the effects of anticoagulants
Antihypertensives (ACE inhibitors and Angiotensin II Antagonists) and diuretics	NSAIDs may reduce the effects of these drugs. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor or Angiotensin II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions should be considered in patients taking a coxib concomitantly with ACE inhibitors or angiotensin II antagonists. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter. Diuretics may increase the risk of nephrotoxicity of NSAIDs/
Antiplatelet agents and selective serotonin reuptake inhibitors (SSRIs)	Increased risk of gastrointestinal bleeding.
Cardiac glycosides	NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.
Ciclosporin	Increased risk of nephrotoxicity.
Corticosteroids	Increased risk of gastrointestinal ulceration or bleeding
Lithium	Decreased elimination of lithium
Methotrexate:	Decreased elimination of methotrexate
Mifepristone	NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone
Quinolone antibiotics	Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions
Tacrolimus	Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus
Zidovudine	Increased risk of haematological toxicity with NSAIDS are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

4.6 Pregnancy and Lactation

Pregnancy

This product is not recommended for use in pregnancy due to the 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. Ibuprofen and its metabolites can pass in very small amounts (0.0008% of the maternal dose) into the breast milk. No harmful effects to infants are known

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, drowsiness, fatigue and visual disturbances. This medicine can impair cognitive function and can affect a patient's ability to drive safely.

4.8 Undesirable effects

- Long term usage & overdosage may cause liver damage
- The most common side effects are nausea and vomiting.
- Other symptoms such as diarrhea, constipation, epigastric pain and burning sensation, dizziness, and skin reactions are to be reported.
- Symptoms of hematemesis, blurred vision, hepatoxicity, and nephrotoxicity have ever been reported.
- It can happen through rarely: lymphophenia, agranulocytosis and hemolytic anemia.

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.

Ibuprofen

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

Body System	Undesirable effect
Nervous system disorders	headache, somnolence, vertigo, fatigue, agitation, dizziness, insomnia, irritability
Gastrointestinal disorders	Gastrointestinal ulcers, sometimes with bleeding and perforation, occult blood loss which may lead to anaemia, melaena, haematemesis, ulcerative stomatitis, colitis, exacerbation of inflammatory bowel disease, complications of colonic diverticula (perforation, fistula)

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.

Ibuprofen

Symptoms and signs

Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely, diarrhoea. Nystagmus, blurred vision, tinnitus, headache and gastrointestinal bleeding may also occur. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as vertigo, dizziness, drowsiness, occasionally excitation and disorientation, loss of consciousness or coma. Occasionally patients develop convulsions. Children may also develop myoclonic cramps. In serious poisoning metabolic acidosis may occur. hypothermia and hyperkalaemia may also occur and the prothrombin time/INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure, liver damage, hypotension, respiratory depression and cyanosis may occur. Exacerbation of asthma is possible in asthmatics.

Treatment

Treatment should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Gastric emptying or oral administration of activated charcoal is indicated if the patient presents within one hour of ingestion of more than 400 mg per kg of body weight. If ibuprofen has already been absorbed, alkaline substances should be administered to promote the excretion of the acid ibuprofen in the urine. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Bronchodilators should be given for asthma. No specific antidote is available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Paracetamol is a well established analgesic and antipyretic.

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.

Ibuprofen is a NSAID that possesses anti-inflammatory, analgesic and antipyretic activity. Animal models for pain and inflammation indicate that ibuprofen effectively inhibits the synthesis of prostaglandins. In humans, ibuprofen reduces pain possibly caused by inflammation or connected with it, swelling and fever. Ibuprofen exerts an inhibitory effect on prostaglandin synthesis by inhibiting the activity of cyclo-oxygenase. In addition ibuprofen has an inhibitory effect on ADP (adenosine diphosphate) or collagen stimulated platelet aggregation.

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.

Caffeine is readily absorbed from the gastro-intestinal tract.

Ibuprofen is rapidly absorbed from the gastrointestinal tract, peak serum concentrations occurring 1-2 hours after administration. Ibuprofen is rapidly distributed throughout the whole body. The plasma protein binding is approximately 99%. Ibuprofen is metabolised in the liver (hydroxylation, carboxylation). The elimination half-life is approximately 2.5 hours in healthy individuals. Pharmacologically inactive metabolites are mainly excreted (90%) by the kidneys but also in bile.

5.3 Preclinical safety data

Not Applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal Silicon Dioxide
Microcrystalline cellulose
Dibasic Calcium Phosphate Anhydrate
FD&C Red No. 3 (Erythrosine)
FD&C Yellow No. 5 (Tartrazine)
FD&C Yellow No. 6 (Sunset Yellow)
Gelatin
Glycerol
Hydroxypropyl Cellulose
Magnesium stearate
Methyl hydroxybenzoate (Nipagin)
Maize starch
Sodium starch glycolate
Propyl hydroxybenzoate (Nipasol)
Sodium Lauryl Sulfate
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.

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Lagos – NIGERIA

Manufacturer

PT. Tempo Scan Pacific

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