1. Name of the Medicinal Product

1.1 Name of the Medicinal Product

NIMEDEX TABLETS

(Aspirin, Acetaminophen & Caffeine Tablets.)

1.2. Strength

Each Uncoated Tablet contains:

Acetaminophen	BP	325mg
Aspirin	BP	250mg
Caffeine (anhydrous)	BP	30mg
Excipients		q.s.

Approved colour used.

1.3. Pharmaceutical Dosage Form

Oral Solid dosage form (Tablet).

2. Qualitative And Quantitative Composition

Qualitative Declaration

The **NIMEDEX TABLETS** contains (Aspirin, Acetaminophen & Caffeine Tablets)

Quantitative Declaration

Composition:

Each Unocated Tablet contains :		
Acetaminophen	BP	275mg
Aspirin	BP	250mg
Caffeine (anhydrous)	BP	30mg
Excipients		q.s.

3. Pharmaceutical Form

Solid dosage form (Tablet).

4. Clinical Particulars

4.1 Therapeutic Indications

For the treatment of mild to moderate pain including headache, migraine, neuralgia, toothache, sore throat, period pains, symptomatic relief of sprains, strains, rheumatic pain, sciatica, lumbago, fibrositis, muscular aches and pains, joint swelling and stiffness, influenza, feverishness and feverish colds.

4.2 Posology and Method of Administration

Posology

Adults, the elderly and young persons aged 16 and over:

2 tablets every 4 hours to a maximum of 8 tablets in 24 hours.

Do not give to children aged under 16 years, unless specifically indicated (e.g. for Kawasaki's disease).

or as directed by the physician.

Method of Administration: For Oral Administration.

4.3 Contraindications

Hypersensitivity to the active ingredients or any of the other constituents. Peptic ulceration and those with a history of peptic ulceration; haemophilia, concurrent anti-coagulant therapy; children under 16 years and when breast feeding because of possible risk of Reyes Syndrome.

4.4 Special Warning and Precautions for Use

Caution should be exercised in patients with asthma, allergic disease, impairment of hepatic or renal function (avoid if severe) and dehydration. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.

Do not take if you have a stomach ulcer.

Do not take more medicine than the label tells you to. If you do not get better, talk to your doctor.

Do not take anything else containing Acetaminophen or paracetamol while taking this medicine.

Talk to your doctor at once if you take too much of this medicine, even if you feel well. This is because too much Acetaminophen or paracetamol can cause delayed, serious liver damage.

There is a possible association between aspirin and Reye's syndrome when given to children. Reye's syndrome is a very rare disease, which affects the brain and liver, and can be fatal. For this reason aspirin should not be given to children under 16 years unless specifically indicated (e.g. Kawasaki's disease).

Patients should be advised that Acetaminophen may cause severe skin reactions. such as skin reddening, blisters, or rash occurs, they should stop use and seek medical assistance right away.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Aspirin

Other NSAIDS and corticosteroids: Concurrent use of other NSAIDS or corticosteroids may increase the likelihood of GI side effects.

Diuretics: Antagonism of the diuretic effect.

Anticoagulants: Increased risk of bleeding due to antiplatelet effect.

Metoclopramide: Metoclopramide increases the rate of absorption of aspirin. However, concurrent use need not be avoided.

Phenytoin: The effect of phenytoin may be enhanced by aspirin. However, no special precautions are needed.

Valproate: The effect of valproate may be enhanced by aspirin.

Methotrexate: Delayed excretion and increased toxicity of methotrexate.

Acetaminophen

Cholestyramine: The speed of absorption of paracetamol is reduced by cholestyramine. Therefore, the cholestyramine should not be taken within one hour if maximal analgesia is required.

Metoclopramide and Domperidone : The speed of absorption of paracetamol is increased by metoclopramide and domperidone. However, concurrent use need not be avoided.

Warfarin: The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

Caffeine

Amphetamine, Dextroamphetamine, Ibuprofen, Alcohol (contained in alcoholic beverages) Amoxicillin, arginine.

4.6 Fertility, pregnancy and lactation

Pregnancy & Lactation:

There is clinical and epidemiological evidence of safety of aspirin in pregnancy, but it may prolong labour and contribute to maternal and neonatal bleeding, and so should not be used in late pregnancy.

Aspirin appears in breast milk, and regular high doses may affect neonatal clotting. Not recommended while breast-feeding due to possible risk of Reye's Syndrome as well as neonatal bleeding due to hypoprothrombinaemia.

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 the doctor regarding its use. Paracetamol is excreted in breast milk but not in a significant amount. Available published data do not contraindicate breast feeding.

Caffeine appears in breast milk. Irritability and poor sleeping pattern in the infant have been reported.

Keep out of reach of children.

4.7 Effects on Ability to Drive and Use Machines

None stated.

4.8 Undesirable Effects

Side effects are mild and infrequent, but there is a high incidence of gastro-intestinal irritation with slight asymptomatic blood loss. Increased bleeding time. Aspirin may precipitate bronchospasm and induce asthma attacks or other hypersensitivity reactions, such as skin reactions (including angioedema and face oedema) in susceptible individuals.

Aspirin may induce gastro-intestinal haemorrhage, occasionally major. It may precipitate gout in susceptible individuals. Possible risk of Reye's Syndrome in children under 16 years.

Adverse effects of paracetamol are rare. Very rare cases of serious skin reactions have been

reported. There have been reports of blood dyscrasias including thrombocytopenia purpura and agranulocytosis, but these were not necessarily causality related to paracetamol.

High doses of caffeine can cause tremor and palpitations.

4.9 Overdose

This product contains both paracetamol and aspirin, and as such, any overdose events should be assessed using information available on both active substances.

• Liver damage is possible in adults who have taken 10g or more of paracetamol. Adults who have consumed more than 5g of paracetamol, may experience liver damage if they have one of the following risk factors:

• Long term treatment with either anti-infectives, anti-epileptics or St John's Wort, or any other drugs that induce liver enzymes.

• likely to be glutathione deplete e.g. eating disorder, cystic fibrosis, HIV infection, starvation, cachexia.

Salicylate poisoning is usually associated with plasma concentrations >350 mg/L (2.5 mmol/L). Most adult deaths occur in patients whose concentrations exceed 700 mg/L (5.1 mol/L). Single doses less than 100 mg/kg are unlikely to cause serious poisoning.

5.0 Pharmacological Properties

5.1 Pharmacodynamic properties

ASPIRIN

Mechanisms of action/effect

Salicylates inhibit the activity of the enzyme cyclo-oxygenase to decrease the formation of precursors of prostaglandins and thromboxanes from arachidonic acid. Although many of the therapeutic effects may result from inhibition of prostaglandin synthesis in various tissues, other actions may also contribute significantly to the therapeutic effects.

Analgesic Produces analgesia through a peripheral action by blocking pain impulse generation and via a central action, possibly in the hypothalamus.

Anti-inflammatory (Non-steroidal) Exact mechanisms have not been determined. Salicylates may act peripherally in inflamed tissue probably by inhibiting the synthesis of prostaglandins and possibly by inhibiting the synthesis and/or actions of other mediators of the inflammatory response.

Antipyretic may produce antipyresis by acting centrally on the hypothalamic heat-regulating centre to produce peripheral vasolidation resulting in increased cutaneous blood flow, sweating and heat loss.

ACETAMINOPHEN

Mechanism of action/effect

Analgesic – the mechanism of analgesic action has not been fully determined. Acetaminophen may act predominantly by inhibiting prostaglandin synthesis in the central nervous system (CNS) and, to a lesser extent, through a peripheral action by blocking pain-impulse generation.

The peripheral action may also be due to inhibition of prostaglandin synthesis or to inhibition of the synthesis or actions of other substances that sensitise pain receptors to mechanical or chemical stimulation.

Antipyretic – paracetamol probably produces antipyresis by acting centrally on the hypothalamic heat-regulation centre to produce peripheral vasodilation resulting in increased blood flow through the skin, sweating, and heat loss. The central action probably involved inhibition of prostaglandin synthesis in the hypothalamus.

CAFFEINE

Mechanisms of action/effect

Central nervous system stimulant – caffeine stimulates all levels of the CNS, although its cortical effects are milder and of shorter duration than those of amphetamines.

Analgesia adjunct Caffeine constricts cerebral vasculature with an accompanying decrease in the cerebral blood flow and in the oxygen tension of the brain. It is believed that caffeine helps to relieve headache by providing more rapid onset of action and/or enhanced pain relief with lower doses of analgesic. Recent studies with ergotamine indicate that the enhancement of effect by the addition of caffeine may also be due to improved gastrointestinal absorption of ergotamine when administered with caffeine.

5.2 Pharmacokinetic properties

ASPIRIN

Absorption and fate

Absorption is generally rapid and complete following oral administration. It is largely hydrolysed in the gastrointestinal tract, liver and blood to salicylate, which is further metabolised primarily in the liver.

ACETAMINOPHEN

Absorption and fate

Acetaminophen is readily absorbed from the gastro-intestinal tract with peak plasma concentrations occurring about 30 minutes to 2 hours after ingestion. It is metabolised in the liver and excreted in the urine mainly as the glucuronide and sulfate conjugates. Less than 5% is excreted as unchanged acetaminophen. The elimination half-life varies from about 1 to 4 hours. Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

A minor hydroxylated metabolite, 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 overdosage and cause liver damage.

CAFFEINE

Absorption and fate

Caffeine is completely and rapidly absorbed after oral administration with peak concentrations occurring between 5 and 90 minutes after dose in fasted subjects. There is no evidence of presystemic metabolism. Elimination is almost entirely by hepatic metabolism in adults.

In adults, marked individual variability in the rate of elimination occurs. The mean plasma elimination half-life is 4.9 hours with a range of 1.9 - 12.2 hours. Caffeine distributes into all body fluids. The mean plasma protein binding of caffeine is 35%.

Caffeine is metabolised almost completely via oxidation, demethylation, and acetylation, and is excreted in the urine as 1-methyluric acid, 1-methylxanthine, 7-methylxanthine, 1,7-dimethylxanthine (paraxanthine). Minor metabolites include 1-methylacrylic acid and 5-acethylamine-6-formylamine-3-methyluracil (AFMU)..

5.3 Preclinical

None Stated.

6.0 Pharmaceutical Particulars

6.1 List of Excipients

- Maize starch BP
- Methyl hydroxybenzoate BP
- Propyl hydroxybenzoate BP
- Gelatin BP
- Microcrystalline cellulose BP
- Purified talc BP
- Stearic acid BP
- Sodium starch glycolate BP
- Crospovidone BP
- Supercoat SC-1010 white IH
- Colour ponceau 4 R supra IH
- Colour poceau 4 R Lake IH
- Dichloromethane BP
- Isopropyl alcohol BP

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

< 36 months>

6.4 Special Precautions for Storage

Store at temperature below 25ºC in a dry place. Protect from light.

6.5 Nature and Contents of Container

10 x10 Tablets packed in a carton along with patient information leaflet.

6.6 Special Precautions for Disposal and Other Handling

None stated.

7. Registrant/Sole agent

EMBASSY PHARMACEUTICAL & CHEMICAL LTD.

41, Ademola Street, South West Ikoyi,

Lagos, Nigeria. Tel.: 01-2900791

8. Manufacturer

LABORATE PHARMACEUTICALS INDIA LIMITED

51, Industrial area, Gondpur, Paonta Sahib, Himachal Pradesh

HO: E-11, Industrial Area, Panipat – 132 103. (INDIA)

9. Date of Revision of Text

To be given after approval of product

10. Dosimetry (If applicable)

Not applicable

11. Instructions for Preparation of Radiopharmaceuticals (If applicable)

Not applicable