1. Name of the Medicinal Product

1.1 (Invented) Name of the Medicinal Product

PARADEX (Acetaminophen and Aspirin Tablets USP)

1.2. Strength

Acetaminophen	USP	500mg
Aspirin	USP	250mg

1.3. Pharmaceutical Dosage Form

Solid Oral Dosage Form: Tablets

2. Qualitative And Quantitative Composition

Qualitative Declaration

PARADEX contains Acetaminophen and Aspirin.

Quantitative Declaration

Each Uncoated Tablets Contains:

Acetaminophen	USP	500mg
Aspirin	USP	250mg
Excipients		q.s.

Approved colour used.

3. Pharmaceutical Form

Tablets

4. Clinical Particulars

4.1 Therapeutic Indications

PARADEX indicated 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

Adults: 2 tablets 3-4 times daily or as directed by the physician.

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

This medication should be avoided in stomach ulcer, any other Acetaminophen containing product. Patients should be advised that Acetaminophen may cause severe skin reactions.

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 Acetaminophen 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 Acetaminophen 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 Acetaminophen with increased risk of bleeding; occasional doses have no significant effect.

Chloramphenicol: Increased plasma concentration of chloramphenicol.

4.6 Pregnancy and 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 Acetaminophen used in the recommended dosage, but patients should follow the advice of the doctor regarding its use. Acetaminophen is excreted in breast milk but not in a significant amount. Available published data do not contraindicate breast feeding.

4.7 Effects on Ability to Drive and Use Machines

None stated

4.8 Undesirable Effects

Skin rashes and other allergic reactions may occur. The rash is usually erythematous or urticarial but sometimes more serious and may be accompanied by fever and mucosal lesions. The use of Acetaminophen has been associated with the occurrence of neutropenia, pancytopenia and leucopoenia.

The most commonly observed adverse events are gastrointestinal in nature: Peptic ulcers, perforation or gastrointestinal bleeding, (sometimes fatal), nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease, gastritis. Bullous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis. Dizziness, oedema, hypertension and cardiac failure may occur in some cases. Some persons especially asthmatics, exhibit notable sensitivity to aspirin which may provoke various hypersensitivity reactions which may include skin eruptions paroxysmal bronchospasm and dyspnoea. It should be administered with caution to patients with impaired renal function, dyspepsia, anaemia and when the patient is dehydrated. Prolonged use of high doses may lead to anaemia, blood dyscrasias, gastrointestinal haemorrhage, peptic ulceration, and renal papillary necrosis.

4.9 Overdose

This product contains both Acetaminophen 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 Acetaminophen. Adults who have consumed more than 5g of Acetaminophen, 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

• regular consumption of ethanol in excess of recommended amounts.

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

5.0 Pharmacological Properties

5.1 Pharmacodynamic Properties

Mechanism of action of Acetaminophen

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 – Acetaminophen 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.

Aspirin

Mechanisms of action/effect

Salicylates inhibit the activity of the enzyme cyco-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 (and consequent reduction of prostaglandin activity) 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.

5.2 Pharmacokinetic Properties

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 Acetaminophen overdosage and cause liver damage.

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.

Drug-Drug Interactions

Drug Interaction of 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.

Drug Intraction of Acetaminophen:

Cholestyramine: The speed of absorption of Acetaminophen 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 Acetaminophen 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 Acetaminophen with increased risk of bleeding; occasional doses have no significant effect.

Chloramphenicol: Increased plasma concentration of chloramphenicol.

5.3 Preclinical Safety Data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the Summary of Product Characteristics.

6.0 Pharmaceutical Particulars

6.1 List of excipients

- ✓ Maize Starch BP
- ✓ Methyl Hydroxybanzoate BP
- ✓ Propyl Hydroxybanzoate BP
- ✓ Gelatin BP
- ✓ Microcrystalline Cellulose BP
- ✓ Colour Apple Green Supra IH
- ✓ Isopropyl Alcohol BP
- ✓ Dichloromethane BP
- ✓ Supercoat (SC-1010) White IH
- ✓ Colour Brilliant Blue Lake IH
- ✓ Colour Tartrazine Lake IH
- ✓ Purified Talc BP
- ✓ Stearic Acid BP
- ✓ Sodium Starch Glycolate BP
- ✓ Crospovidone BP
- ✓ Colloidal Anhydrous Silica BP
- ✓ Purified Water BP

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

<36 Months>

6.4 Special Precautions for Storage

Store at a temperature exceeding 25°C. Protect from light.

Keep all medicines out of reach of the children.

6.5 Nature and Contents of Container

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

6.6 Special Precautions for Disposal and Other Handling

No special requirements.

7.0 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, H.P. (INDIA)

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

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