## 1.6 PRODUCT INFORMATION

### 1.6.1 SUMMARY OF PRODUCT CHARACTERISTICS

**1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT**
PHARMADEX (Paracetamol, Aspirin & Caffeine Caplets)

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**
Each caplet contains:
Paracetamol BP 325 mg
Aspirin BP 400 mg
Caffeine BP 30 mg
Excipients QS

**3. PHARMACEUTICAL FORM**
Tablet, Solid dosage form

**4. CLINICAL PARTICULARS**
**4.1 Therapeutic indications**
Pharmadex can be used to relief from mild including headache, migraine, neuralgia, toothache, headache, sore throats, period pains and 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**
Adult: 1 to 2 caplets
Children 12 years and over: 1 Caplet
Repeat dosage three or four times a day if necessary or
As directed by the Physician

**Method of administration:**
Oral use.

**4.3 Contraindications**
Contraindicated in Hypersensitivity to the active substance or to any of the excipients

**4.4 Special warnings and precaution for use**
If the patient has a contraindication to one component, then the combination is contraindicated.
**Caffeine**
Should be used in caution with the following conditions:
When used with isoflurane in premature infants; a clinical study on mice showed that caffeine increases the toxicity of isoflurane when used together.
When used with adolescents at high risk of repetitive mild traumatic brain injury; a study showed that chronic caffeine consumption might alter the recovery from it.
When used in people who have a positive family history of Meniere disease; a study showed that caffeine might lower the age of onset of symptoms in this disease.

**Acetaminophen**
Should be used with caution and in reduced doses (2 to 3 grams per day) in patients with hepatic impairment for a period not exceeding a few days.
Patients with chronic hepatitis C infection have a predisposition to develop liver failure after acetaminophen overdose. Also, Acetaminophen showed a dose-dependent enhancement of the anticoagulant effect of warfarin, although studies in healthy volunteers have shown no such effect. Competition for CYP1A2 and 3A4 hypothesizes it, but conditions such as aging and tissue hypoxia alter the activity of these pathways in human studies. Acetaminophen still is the analgesic and antipyretic of choice in patients who take warfarin, but excessive amounts and prolonged administration (greater than 1.3 grams per day for 2 weeks) should be avoided.

**Aspirin**
Contraindicated in:
Children under the age of 12 because of the risk of Reye syndrome, except with Kawasaki disease
An aspirin-exacerbated respiratory disease which is a chronic rhinosinusitis, nasal polyps, asthma, and acute reaction after ingestion of aspirin. However, when aspirin is needed as a therapy, aspirin desensitization is the most relevant therapeutic approach that improves the nasal symptoms and appears to stabilize intrinsic asthma.
Patients with peptic ulcer disease since aspirin is injurious to the mucosa of stomach and duodenum by inhibiting prostaglandin synthesis. Patients who need to take aspirin should use it with caution, and a proton pump inhibitor may be used during the treatment period.

**4.5 Interaction with other medicinal products and other forms of interaction**
This drug should not be used with the following medications
acetazolamide, cimetidine, corticosteroids (e.g., prednisone), ketoconazole, methotrexate, certain medications for gout (e.g., probenecid, sulfinpyrazone), antiseizure drugs (e.g., phenytoin, valproic acid), vemurafenib.
This medication may increase the risk of bleeding when taken with other drugs that also may cause bleeding. Examples include anti-platelet drugs such as clopidogrel, "blood thinners" such as dabigatran/enoxaparin/warfarin, among others.
Consult your doctor before using this product if you have recently received certain live vaccines (e.g., varicella vaccine, influenza intranasal vaccine).
Check all prescription and nonprescription medicine labels carefully since many contain pain relievers/fever reducers (acetaminophen, aspirin, or NSAIDs such as ibuprofen, celecoxib, naproxen) and if taken together with this product, may increase your risk for side effects. However, if your doctor has directed you to take low-dose aspirin for heart attack or stroke prevention (usually at dosages of 81-325 milligrams a day), you should continue taking it unless your doctor instructs you otherwise.

**4.6 Pregnancy and Lactation**
Ask a health professional before use. It is especially important not to use aspirin during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.
Use of acetaminophen; aspirin, ASA; caffeine combination products are only recommended during breast-feeding if the benefits to the mother outweigh the potential risks to the infant. The American Academy of Pediatrics (AAP) recommends that aspirin-containing products be used cautiously during breastfeeding.
Alternative analgesics and antipyretics considered to be usually compatible with breast-feeding by the AAP include acetaminophen and ibuprofen, when used as single ingredients. Multi-ingredient products such as acetaminophen; aspirin; caffeine are generally not preferred options. Peak caffeine

milk levels usually occur within 1 hour after the maternal ingestion of a caffeinated product; with milk: plasma ratios of 0.5—0.7 reported. Although only small amounts are secreted in breast milk, caffeine can accumulate in the neonate if maternal ingestion is moderate to high. Higher caffeine intake (> 500 mg/day) by a nursing mother may cause irritability or poor sleeping patterns in the infant who is breast-feeding. Nursing mothers should limit their intake of caffeine if possible. Additionally, mothers who are breast-feeding infants who are prescribed caffeine for apnea should avoid additional caffeine. Salicylates such as aspirin are excreted into breast milk and could cause adverse effects in infants. Mean peak breast milk concentrations of salicylate in 6 nursing mothers after aspirin doses of 500, 1000, and 1500 mg were 5.8, 15.8, and 38.8 mg/L, respectively. Salicylate levels were detectable in breast milk within 1 hour of dosing and reached maximum concentration within 2—6 hours.
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. Bronchospasm and skin reactions in hypersensitive patients.

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.

**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
• regular consumption of ethanol in excess of recommended amounts
• 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 mmol/L). Single doses less than 100 mg/kg are unlikely to cause serious poisoning.
Symptoms
Common features exist for both active substances when taken in overdose, but these can be tabulated as follows:

| Paracetamol | Aspirin | Caffeine |
|---|---|---|
| Within the first 24 hours:<br>Pallor<br>Nausea | Common:<br>Vomiting, Dehydration, Tinnitus<br>Vertigo, Deafness, Sweating<br>Warm extremities with bounding pulses Increased | Other symptoms of overdosage, associated with the caffeine |

| | | |
|---|---|---|
| Vomiting<br>Anorexia<br>Abdominal pain<br>After 12-48 hours:<br>Liver damage<br>Abnormalities of glucose metabolism and metabolic acidosis<br>Severe poisoning:<br>Hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema and death.<br>With or without severe liver damage:<br>Acute renal failure with acute tubular necrosis strongly suggested by loin pain haematuria and proteinuria.<br>Cardiac arrhythmias<br>Pancreatitis | respiratory rate<br>Hyperventilation<br>Acid base disturbance<br>Mixed respiratory alkalosis and metabolic acidosis with normal or high arterial pH (normal or reduced hydrogen ion concentration) in adults and children aged over 4 years.<br>In children aged 4 years or less, a dominant metabolic acidosis with low arterial pH (raised hydrogen ion concentration) is common.<br>Acidosis can increase salicylate transfer across the blood brain barrier.<br>Uncommon:<br>Haematemesis<br>Hyperpyrexia<br>Hypoglycaemia<br>Hypokalaemia<br>Thrombocytopenia<br>Increased INR/PTR<br>Intravascular coagulation<br>Renal failure<br>Non-cardiac pulmonary oedema<br>Confusion, disorientation, coma and convulsions are more common in children than adults. | component, include:<br>CNS stimulation; anxiety, nervousness, restlessness, insomnia, excitement, muscle twitching, confusion, convulsions<br>Cardiac: tachycardia, cardiac arrhythmia<br>Gastric: Abdominal or stomach pains<br>Other: diuresis, facial flushing |

Management

Paracetamol:

Immediate treatment is essential in the management of overdose due to the paracetamol content of the product.

There may be few or no initial symptoms, and these can 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 concentrations 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, or are under 10 years or over 70, beyond 24h from ingestion should be discussed with the National Poisons Information Service (NPIS) or a liver unit.

Salicylates:

Treatment with activated charcoal should be considered if salicylate plasma concentration is greater than 250mg/kg.

Plasma salicylate concentrations should be measured although the severity of poisoning cannot be determined from this alone and the clinical and biochemical features must be taken into account.

Elimination of aspirin is increased by urinary alkalinisation, which is achieved by the administration of 1.26% sodium bicarbonate. The urine pH should be monitored. Metabolic acidosis should be

corrected with intravenous 8.4% sodium bicarbonate (first check serum potassium). Forced diuresis should not be used since it does not enhance salicylate excretion and may cause pulmonary oedema.
Haemodialysis is the treatment of choice for severe poisoning and should be considered in patients with plasma salicylate concentrations >700 mg/L (5.1 mmol/L), or lower concentrations associated with severe clinical or metabolic features.
Patients under 10 years or over 70 years of age may be at an increased risk of salicylate toxicity and may require dialysis at an earlier stage.
Caffeine:
Treatment of caffeine overdose is primarily symptomatic and supportive. Diuresis should be treated by maintaining fluid and electrolyte balance and CNS symptoms can be controlled by intravenous administration of diazepam.

## 5. PHARMACOLOGICAL PROPERTIES

**Pharmacotherapeutic group:** Analgesics and Antipyretics
**ATC code:** N02BE01

### 5.1 Pharmacodynamic properties

**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.

**PARACETAMOL**
Mechanism of action/effect
Analgesic – the mechanism of analgesic action has not been fully determined. Paracetamol 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.
**Paracetamol**
Absorption and fate
Paracetamol 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 paracetamol. 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 safety data**
There are no preclinical data of relevance to the prescribe which are additional to that already included in other sections

**6. PHARMACEUTICAL PARTICULARS**
**6.1 List of Excipients**
Citric Acid Anhydrous BP
Maize Starch BP
Crosspovidone BP
PVPK-30 BP
Isopropyl Alcohol BP
Colloidal Silicon Dioxide BP
Stearic Acid BP
Purified Talc BP

**6.2 Incompatibilities**
Not applicable

**6.3 Shelf life**
36 months

**6.4 Special precautions for storage**
Store below $30^0$ C. Protect from light and moisture.
**Keep Medicine Out of Reach of Children**

**6.5 Nature and contents of container**
10 Blisters of 10 tablets each are packed in carton along with Product insert. (10×10's Alu-PVC Blisters pack)

**7. MARKETING AUTHORISATION HOLDER**

**Star Biotech Limited**

Address: 1st floor, Prestige House, Rwandex, Kigali-Rwanda

Telephone: (+250) 785377688 / (+250) 787229914

Email: shantilal.bhanderi@yahoo.com

**8. MARKETING AUTHORISATION NUMBER**
Not Applicable

**9. DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION**
Not Applicable