SUMMARY PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

Coldril Capsules

Pharmaceutical Form

Capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Qualitative declaration

Pseudoephedrine Hydrochloride, Paracetamol and Chlorpheniramine Maleate.

Quantitative Declaration

Each capsule contains:

Pseudoephedrine Hydrochloride 30mg,

Paracetamol 500mg

Chlorpheniramine Maleate .....2mg.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Capsule

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Coldril is indicated in cold, flu, nasal congestion and associated fever, body ache and headache.

4.2 Posology and Method of Administration

Dosage

As directed by the Physician OR

Not recommended for children under 12 years.

12 years and above - 2 capsules maximum 8 capsules in 24hours.

Method of Administration

For oral administration only

4.3 Contraindications

Pseudoephedrine Hydrochloride

Coldril Capsules should not be used in patients hypersensitive to pseudoephedrine or any of the other ingredients. Patients receiving monoamine oxidase inhibitors or who have received these agents in the last two weeks. Patients using other sympathomimetic decongestants or beta-blockers. (See Section 4.5).

Patients with cardiovascular disease including ischaemic heart disease, occlusive vascular disease and hypertension.

Coldril Capsules is contraindicated in patients with:

- Severe renal impairment
- Phaeochromocytoma
- Diabetes
- Hyperthyroidism
- Closed angle glaucoma
- Severe hypertension or uncontrolled hypertension
- Severe acute or chronic kidney disease/renal failure.

Chlorpheniramine Maleate

Acute asthma, hypersensitivity to any of the ingredients or other antihistamines. Premature infants or neonates because of their increased susceptibility to antimuscarinic effects. Coldril Capsules should not be given to patients taking monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping such treatment ***Paracetamol***

This product should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal (see Interactions with other medicinal products and other forms of interaction).

- Severe hepatic impairment.
- Epilepsy not controlled by treatment.

4.4 Special Warnings and Precautions

Pseudoephedrine Hydrochloride

Patients with thyroid disease who are receiving thyroid hormones should not take pseudoephedrine unless directed by a physician.

Patients with the following conditions should be advised to consult a physician before using this product: difficulty in urination and/or enlargement of the prostate; a respiratory condition such as emphysema, chronic bronchitis or acute or chronic bronchial asthma.

This product should not be used for persistent or chronic cough, such as occurs with asthma, or emphysema where cough is accompanied by excessive secretions, unless directed by a physician.

Patients should be advised to consult a physician if their cough lasts for more than 5 days or comes back, or is accompanied by a fever, rash or persistent headache.

Caution should be exercised when using the product in the presence of severe hepatic impairment or moderate to severe renal impairment (particularly if accompanied by cardiovascular disease), [See section 5.2], or occlusive vascular disease.

If any of the following occur, this product should be stopped

- Hallucinations
- Restlessness
- Sleep disturbances

Severe Skin reactions: Severe skin reactions such as acute generalized exanthematous pustulosis (AGEP) may occur with pseudoephedrine-containing products. This acute pustular eruption may occur within the first 2 days of treatment, with fever, and numerous, small, mostly non-follicular pustules arising on a widespread edematous erythema and mainly localized on the skin folds, trunk, and upper extremities. Patients should be carefully monitored. If signs and symptoms such as pyrexia, erythema, or many small pustules are observed, administration of this medicine should be discontinued, and appropriate measures taken if needed.

Ischaemic colitis: Some cases of ischemic colitis have been reported with pseudoephedrine. Pseudoephedrine should be discontinued, and medical advice sought if sudden abdominal pain, rectal bleeding or other symptoms of ischemic colitis develop.

Ischaemic optic neuropathy: Cases of ischemic optic neuropathy have been reported with pseudoephedrine.

Pseudoephedrine should be discontinued if sudden loss of vision or decreased visual acuity such as scotoma occurs.

Posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS): Cases of PRES and RCVS have been reported with the use of pseudoephedrine-containing products. The risk is increased in patients with severe or uncontrolled hypertension, or with severe acute or chronic kidney disease/renal failure as these are risk factors for developing PRES or RCVS.

Pseudoephedrine should be discontinued, and immediate medical assistance sought if the following symptoms occur: sudden severe headache or thunderclap headache, nausea, vomiting, confusion, seizures and/or visual disturbances. Most reported cases of PRES and RCVS resolved following discontinuation and appropriate treatment.

Not more than 4 doses should be given in any 24 hours.

Do not exceed the stated dose.

Do not take with any other cough and cold medicine.

Chlorpheniramine Maleate

Coldril Capsules should be given with caution to patients with epilepsy, severe cardiovascular disorders, liver disorders, renal impairment, glaucoma, urinary retention, prostatic enlargement, pyloroduodenal obstruction, asthma, bronchitis, bronchiectasis, thyrotoxicosis and severe hypertension.

Special care should be taken when using chlorpheniramine Maleate in children and the elderly as they are more likely to experience the neurological anticholinergic effects and paradoxical excitation (e.g. Increased energy, restlessness, nervousness).

The anticholinergic properties of chlorphenamine may cause drowsiness, dizziness, blurred vision and psychomotor impairment in some patients which may seriously affect ability to drive and use machinery.
The effects of alcohol may be increased and therefore concurrent use should be avoided.
If symptoms do not go away within 5 days talk to your pharmacist or doctor.
Keep all medicines out of the reach and sight of children.
Although most antihistamines should be avoided by patients with porphyria, chlorpheniramine Maleate has been used and is thought to be safe.
Should not be used with other antihistamine containing products, including antihistamine containing cough and cold medicines.
Concurrent use with drugs which cause sedation such as anxiolytics and hypnotics may cause an increase in sedative effects, therefore medical advice should be sought before taking chlorphenamine concurrently with these medicines.

Paracetamol
This product contains Paracetamol which may be fatal in overdose. In the event of overdosage or suspected overdose and notwithstanding the fact that the person may be asymptomatic, the nearest doctor, hospital or Poison Centre must be contacted immediately.
Dosages in excess of those recommended may cause severe liver damage.
Note: This does not exclude the inclusion of further information. Other information required under 'Warnings' is not addressed here.
In adults and adolescents 12 years and older:
The maximum dose of 8 tablets of Paracetamol should not be exceeded. In order to avoid inadvertent overdose, patients should be advised not to exceed the recommended dose and not to use any other Paracetamol (including over the counter) or tramadol hydrochloride containing products concurrently without the advice of a physician.
In severe renal insufficiency (creatinine clearance <10 ml/mm), Paracetamol is not recommended.
In patients with severe hepatic impairment Paracetamol should not be used (see Contraindications).
The hazards of Paracetamol overdose are greater in patients with non-cirrhotic alcoholic liver disease.
In moderate cases prolongation of dosage interval should be carefully considered.
In severe respiratory insufficiency, Paracetamol is not recommended.
Paracetamol is not suitable as a substitute in opioid-dependent patients.
Concomitant use of opioid agonists-antagonists (nalbuphine, buprenorphine, pentazocine) is not recommended (see Interactions with other medicinal products and other forms of interaction).

Special Precautions

Paracetamol should be used with caution in opioid dependent patients, or in patients with cranial trauma, in patients prone to convulsive disorder, biliary tract disorders, in a state of shock, in an altered state of consciousness for unknown reasons, with problems affecting the respiratory center or the respiratory function, or with an increased intracranial pressure.

Paracetamol in overdosage may cause hepatic toxicity in some patients.

Symptoms of withdrawal reactions, similar to those occurring during opiate withdrawal may occur (see Undesirable effects).

4.5 Interaction with other Drugs and other Forms of Interaction

Pseudoephedrine Hydrochloride

MAOIs and/or RIMAs: Should not be given to patients taking MAOIs or within 14 days of stopping treatment:

increased risk of hypertensive crisis

- Moclobemide: risk of hypertensive crisis.
- Antihypertensives (including adrenergic neuron blockers & beta-blockers): this product may block the hypotensive effects.
- Cardiac glycosides: increased risk of dysrhythmias
- Ergot alkaloids (ergotamine & methergine): increased risk of ergotism
- Appetite suppressants and amphetamine-like psychostimulants: risk of hypertension
- Oxytocin – risk of hypertension
- Enhances effects of anticholinergic drugs (such as TCAs).

Chlorpheniramine Maleate

There may be an interaction between chlorpheniramine and any of the following:

- alcohol
- barbiturates (e.g., phenobarbital, pentobarbital)
- benzodiazepines (e.g., lorazepam, diazepam)
- clarithromycin
- erythromycin
- ketoconazole
- MAO inhibitors (e.g., phenelzine, tranylcypromine, moclobemide)
- Medications with anticholinergic effects (e.g., benztropine, diphenhydramine

Paracetamol

Concomitant use is contraindicated with:

- Non-selective MAO Inhibitors

Risk of serotoninergic syndrome: diarrhoea, tachycardia, sweating, trembling, confusion, even coma.

Selective-A MAO Inhibitors

- Extrapolation from non-selective MAO inhibitors

Risk of serotoninergic syndrome: diarrhoea, tachycardia, sweating, trembling, confusion, even coma.

- Selective-B MAO Inhibitors

Central excitation symptoms evocative of a serotoninergic syndrome: diarrhoea, tachycardia, sweating, trembling, confusion, even coma.

Concomitant use is not recommended with:

- Alcohol

Alcohol increases the sedative effect of opioid analgesics.

The effect on alertness can make driving of vehicles and the use of machines dangerous.

Avoid intake of alcoholic drinks and of medicinal products containing alcohol.

- Carbamazepine and other enzyme inducers

Risk of reduced efficacy and shorter duration due to decreased plasma concentrations of tramadol.

- Opioid agonists-antagonists (buprenorphine, nalbuphine, pentazocine)

Decrease of the analgesic effect by competitive blocking effect at the receptors, with the risk of occurrence of withdrawal syndrome.

Concomitant use which needs to be taken into consideration:

- In isolated cases there have been reports of Serotonin Syndrome in a temporal connection with the therapeutic use of tramadol in combination with other serotoninergic medicines such as selective serotonin re-uptake inhibitors (SSRIs) and triptans. Signs of Serotonin Syndrome may be for example, confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus and diarrhea.
- Other opioid derivatives (including antitussive drugs and substitutive treatments), benzodiazepines and barbiturates
- Increased risk of respiratory depression which can be fatal in cases of overdose.
- Other central nervous system depressants, such as other opioid derivatives (including antitussive drugs and substitutive treatments), barbiturates, benzodiazepines, other anxiolytics, hypnotics, sedative antidepressants, sedative antihistamines, neuroleptics, centrally acting antihypertensive drugs, thalidomide and baclofen.

These medicines can cause increased central depression. The effect on alertness can make driving of vehicles and the use of machines dangerous.

As medically appropriate, periodic evaluation of prothrombin time should be performed when Paracetamol/tramadol and warfarin like compounds are administered concurrently due to reports of increased INR.

Other medicines known to inhibit CYP3A4, such as ketoconazole and erythromycin, might inhibit the metabolism of tramadol (N-demethylation) probably also the metabolism of the active O-demethylated metabolite.

Medicinal products reducing the seizure threshold, such as bupropion, serotonin reuptake inhibitor antidepressants, tricyclic antidepressants and neuroleptics. Concomitant use of tramadol with these drugs can increase the risk of convulsions. The speed of absorption of Paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine.

Pre- or postoperative application of the antiemetic 5-HT3 antagonist ondansetron increases the requirement of tramadol in patients with postoperative pain.

4.6 Fertility, Pregnancy and Lactation

Pregnancy

Pseudoephedrine Hydrochloride

There are limited data from the use of Pseudoephedrine Hydrochloride in pregnant women. It is advised that Pseudoephedrine Hydrochloride should be avoided during pregnancy, particularly during the first trimester, as defective closure of the abdominal wall (gastroschisis) has been reported very rarely in new-borns after first trimester exposure.

Lactation

Pseudoephedrine Hydrochloride has been detected in human milk with a small percentage of the total maternal dose potentially administered to the suckling infant. The use of pseudoephedrine should be avoided during breast feeding as lactation may be suppressed, and irritability and disturbed sleep have been reported in breast fed infants. **Pregnancy**

Chlorphenamine Maleate

There are no adequate data from the use of chlorphenamine Maleate in pregnant women. The potential risk for humans is unknown. Use during the third trimester may result in reactions in the newborn or premature neonates. Not to be used during pregnancy unless considered essentially by a physician.

Lactation

Chlorphenamine Maleate and other antihistamine may inhibit lactation and may be secreted in breast milk. Not to be used during lactation unless considered essential by a physician.

Pregnancy

Paracetamol

Since Paracetamol is a fixed combination of active ingredients including tramadol, it should not be used during pregnancy.

Epidemiological studies in human pregnancy have shown no ill effects due to Paracetamol used in the recommended dosages.

Lactation

Since Paracetamol is a fixed combination of active ingredients including tramadol, it should not be ingested during breast feeding.

Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast feeding by women using single ingredient medicinal products containing only Paracetamol.

4.7 Effect on Ability to Drive and Use Machines

Coldril Capsules contain Chlorphenamine Maleate may cause drowsiness and dizziness in some persons and its use constitutes a danger to patients who drive vehicles or work with moving machineries.

4.8 Adverse Effects

Pseudoephedrine Hydrochloride

The following side effects may be associated with the use of Pseudoephedrine Hydrochloride:
(frequencies not known cannot be estimated from the available data).

- **Immune system disorders:**

Hypersensitivity reactions – cross-sensitivity may occur with other sympathomimetics.

- **Psychiatric disorders:**

Hallucinations (particularly in children), insomnia, sleep disturbances, anxiety, restlessness, irritability, excitability, psychotic disorder has occurred rarely following misuse of pseudoephedrine.

- **Nervous system disorders:**

Headache, tremor, dry mouth.

- **Eye disorders:**

Angle-closure glaucoma.

- **Cardiac disorders:**

Tachycardia, palpitations, arrhythmia.

- **Vascular disorders:**

Hypertension impaired circulation to the extremities.

- **Gastrointestinal disorders:**

Nausea, vomiting, ischaemic colitis.

- **Skin and subcutaneous tissue disorders:**

Fixed drug eruption in the form of erythematous nodular patches, rash. Severe skin reactions, including acute generalized exanthematous pustulosis (AGEP).

- **Renal and urinary disorders:**

Urinary retention.

- **Posterior reversible encephalography syndrome:**

See Section 4.4.

- **Reversible cerebral vasoconstriction syndrome:**

See Section 4.4.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

Chlorphenamine Maleate

The following convention has been utilised for the classification of the frequency of adverse reactions: very common (>1/10), common (>1/100 to <1/10), uncommon (>1/1000 to <1/100), rare (>1/10,000 to <1/1000) and very rare (<1/10,000), not known (cannot be estimated from available data).

Adverse reactions identified during post-marketing use with chlorphenamine are listed below. As these reactions are reported voluntarily from a population of uncertain size, the frequency of some reactions is unknown but likely to be rare or very rare.

Paracetamol

- Adverse effects of Paracetamol are rare but hypersensitivity including skin rash may occur. There have been reports of blood dyscrasias including thrombocytopenia and agranulocytosis, but these were not necessarily causally related to Paracetamol.
- There have been several reports that suggest that Paracetamol may produce hypoprothrombinemia when administered with warfarin-like compounds. In other studies, prothrombin time did not change.

'**Reporting of suspected adverse reactions:** Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org'

4.9 Overdose

Pseudoephedrine Hydrochloride

Symptoms and signs

The symptoms of overdose include irritability, nervousness, tremor, cardiac arrhythmias, palpitations, tachycardia, convulsions, urinary retention and hypertension, restlessness, dry mouth, anxiety, insomnia, nausea, vomiting and possible tolerance to Pseudoephedrine Hydrochloride.

Treatment

Overdose should be treated by general supportive measures. Respiratory and circulatory function should be maintained by supportive measures. Catheterisation of the bladder may be required.

The benefit of gastric decontamination is uncertain. Consider activated charcoal (charcoal dose: 50 g for adults; 1g/kg for children). Optimal effects are within 1 hour of ingestion of more than a toxic dose. Volunteer studies suggest that there is reduced absorption within 2 hours and efficacy declines thereafter. Alternatively consider gastric lavage in adults within 1 hour of a potentially life-threatening overdose. Monitor pulse, blood pressure and cardiac rhythm. Treat any hypertension or convulsions as necessary.

Asymptomatic patients should be observed for 4 hours or 8 hours if a slow-release product has been taken.

Chlorphenamine Maleate

Symptoms and signs

The estimated lethal dose of chlorphenamine is 25 to 50mg/kg body weight. Symptoms and signs include sedation, paradoxical excitation of the CNS, toxic psychosis, convulsions, apnoea, anticholinergic effects, dystonic reactions and cardiovascular collapse including arrhythmias.

Treatment

Management should be as clinically indicated or as recommended by the national poisons centers where available.

Symptomatic and supportive measures should be provided with special attention to cardiac, respiratory, renal and hepatic functions and fluid and electrolyte balance. If overdosage is by the oral route, treatment with activated charcoal should be considered provided there are no contraindications for use and the overdose has been taken recently (treatment is most effective if given within an hour of ingestion). Treat hypotension and arrhythmias vigorously. CNS convulsions may be treated with i.v. diazepam. Haemoperfusion may be used in severe cases.

Paracetamol

Symptoms and signs

An overdose is of particular concern in young children. 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. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalophathy, coma and death. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Liver damage is possible in adults who have taken 7.5-10 g or more of Paracetamol. It is considered that excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of Paracetamol are ingested), become irreversibly bound to liver tissue.

Treatment

Information specific to Paracetamol overdose:

Immediate treatment is essential in the management of Paracetamol overdose. Despite a lack of signific

attention and any adult or adolescent who had ingested around 7.5 g or more of Paracetamol in the preceding 4 hours or any child who has ingested 150 mg/kg of Paracetamol in the preceding 4 hours should undergo gastric lavage. An initial dose of 150 mg/kg N-acetylcysteine in 200 ml dextrose injection given intravenously over 15 minutes, followed by an infusion of 50 mg/kg in 500 ml dextrose injection over the next four hours, and then 100 mg/kg in 1 000 ml dextrose injection over the next sixteen hours. The volume of intravenous fluid should be modified for children.

Although the oral formulation is not the treatment of choice, 140 mg/kg dissolved in water may be administered initially, followed by 70 mg/kg every four hours for seventeen doses.

A plasma Paracetamol level should be determined four hours after ingestion in all cases of suspected overdosage. Levels done before four hours, unless high, may be misleading. Patients at risk of liver damage, and hence requiring continued treatment with N-acetylcysteine, can be identified according to their plasma Paracetamol level. The plasma Paracetamol level can be plotted against time since ingestion in the normogram below. The normogram should be used only in relation to a single acute ingestion.

Administration of oral methionine or intravenous N-acetylcysteine (NAC) which may have a beneficial effect up to at least 48 hours after the overdose, may be required. Administration of intravenous NAC is most beneficial when initiated within 8 hours of overdose ingestion. However, NAC should still be given if the time to presentation is greater than 8 hours after overdose and continued for a full course of therapy. NAC treatment should be started immediately when massive overdose is suspected. General supportive measures must be available.

Irrespective of the reported quantity of Paracetamol ingested, the antidote for Paracetamol, NAC, should be administered orally or intravenously, as quickly as possible, if possible, within 8 hours following the overdose

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group and ATC Code

Pharmacotherapeutic group: **Cold preparation without Anti-infective.**

ATC Code: **R05A**

Mechanism of action

Pseudoephedrine Hydrochloride

Pseudoephedrine Hydrochloride is a phenethylamine and a diastereomer of ephedrine with sympathomimetic property. Pseudoephedrine displaces norepinephrine from storage vesicles in presynaptic neurones, thereby releasing norepinephrine into the neuronal synapses where it stimulates primarily alpha-adrenergic receptors. It also has weak direct agonist activity at alpha- and beta- adrenergic receptors. Receptor stimulation results in vasoconstriction and decreases nasal and sinus congestion.

Chlorpheniramine Maleate

Chlorpheniramine Maleate competes with histamine for histamine H1-receptor sites on smooth muscles of the bronchi, gastrointestinal tract, uterus and large blood vessels; it binds to cellular receptors, preventing access of histamine, thereby suppressing histamine-induced allergic symptoms. Chlorpheniramine does not directly alter histamine or its release.

Paracetamol

According to its FDA labeling, Paracetamol's exact mechanism of action has not been fully established Label - despite this, it is often categorized alongside NSAIDs (nonsteroidal anti-inflammatory drugs) due to its ability to inhibit the cyclooxygenase (COX) pathways.14 It is thought to exert central actions which ultimately lead to the alleviation of pain symptoms.

One theory is that Paracetamol increases the pain threshold by inhibiting two isoforms of cyclooxygenase, COX-1 and COX-2, which are involved in prostaglandin (PG) synthesis. Prostaglandins are responsible for eliciting pain sensations. Paracetamol does not inhibit cyclooxygenase in peripheral tissues and, therefore, has no peripheral anti-inflammatory effects. Though acetylsalicylic acid (aspirin) is an irreversible inhibitor of COX and directly blocks the active site of this enzyme, studies have shown that Paracetamol (paracetamol) blocks COX indirectly.24 Studies also suggest that Paracetamol selectively blocks a variant type of the COX enzyme that is unique from the known variants COX-1 and COX-2. This enzyme has been referred to as COX-3. The antipyretic actions of Paracetamol are likely attributed to direct action on heat-regulating centers in the brain, resulting in peripheral vasodilation, sweating, and loss of body heat. The exact mechanism of action of this drug is not fully understood at this time, but future research may contribute to deeper knowledge.

Pharmacodynamic effects

Pseudoephedrine Hydrochloride

Pseudoephedrine Hydrochloride is a sympathomimetic agent, structurally similar to ephedrine, used to relieve nasal and sinus congestion and reduce air-travel-related otalgia in adults. The salts pseudoephedrine hydrochloride and pseudoephedrine sulfate are found in many over-the-counter

preparations either as single-ingredient preparations, or more commonly in combination with antihistamines and/or Paracetamol/ibuprofen. Unlike antihistamines, which modify the systemic histamine-mediated allergic response, pseudoephedrine only serves to relieve nasal congestion commonly associated with colds or allergies. The advantage of oral pseudoephedrine over topical nasal preparations, such as oxymetazoline, is that it does not cause rebound congestion (rhinitis medicamentosa).

Chlorpheniramine Maleate

In allergic reactions an allergen interacts with and cross-links surface IgE antibodies on mast cells and basophils. Once the mast cell-antibody-antigen complex is formed, a complex series of events occurs that eventually leads to celldegranulation and the release of histamine (and other chemical mediators) from the mast cell or basophil. Once released, histamine can react with local or widespread tissues through histamine receptors. Histamine, acting on H1-receptors, produces pruritis, vasodilatation, hypotension, flushing, headache, tachycardia, and bronchoconstriction. Histamine also increases vascular permeability and potentiates pain. Chlorpheniramine, is a histamine H1 antagonist (or more correctly, an inverse histamine agonist) of the alkylamine class. It competes with histamine for the normal H1-receptor sites on effector cells of the gastrointestinal tract, blood vessels and respiratory tract. It provides effective, temporary relief of sneezing, watery and itchy eyes, and runny nose due to hay fever and other upper respiratory allergies.

Paracetamol

Animal and clinical studies have determined that Paracetamol has both antipyretic and analgesic effects. This drug has been shown to lack anti-inflammatory effects. As opposed to the *salicylate* drug class, Paracetamol does not disrupt tubular secretion of uric acid and does not affect acid-base balance if taken at the recommended doses. Paracetamol does not disrupt hemostasis and does not have inhibitory activities against platelet aggregation. Allergic reactions are rare occurrences following Paracetamol use.

5.2 Pharmacokinetic Properties

Pseudoephedrine Hydrochloride

Pseudoephedrine Hydrochloride is rapidly and completely absorbed after oral administration. After an oral dose of 180 mg to man, peak plasma concentrations of 500-900 ng/ml were obtained about 2 hours post dose. The plasma half-life was about 5.5 hours and was increased in subjects with alkaline urine and decreased in subjects with acid urine. The only metabolism was N-demethylation which occurred to a small extent. Excretion was mainly via the urine.

Chlorpheniramine Maleate

Chlorpheniramine Maleate is absorbed relatively slowly from the gastro – intestinal tract, peak plasma concentrations occurring about 2.5 to 6 hours after administration by mouth. Bioavailability is low, values of 25 to 50% having been reported. Chlorpheniramine appears to undergo considerable first – pass metabolism. About 70% of chlorpheniramine in the circulation is bound to plasma proteins. There is wide inter -individual variations in pharmacokinetics of chlorpheniramine. Values ranging from 2to 43 hours have been reported for the half-life. Chlorpheniramine is widely distributed in the body including passage into CNS. Chlorpheniramine Maleate is extensively metabolized. Unchanged drug and metabolites are excreted primarily in the urine. Only trace amounts have been found in the feaces. Ammonium chloride is absorbed from the gastro- intestinal tract. The ammonium ICN is converted into urea in the liver the anion thus liberated into the blood stream and extracellular fluid causes a metabolic acidosis and decreases the PH of the urine; this is followed by transient dieresis. Sodium citrate is metabolized, after absorption, to bicarbonate.

Paracetamol

Absorption: Paracetamol is readily absorbed from the gastrointestinal tract.

Distribution: peak plasma concentrations occur about 10 to 60 minutes after oral doses. Paracetamol is distributed into most body tissues. It crosses the placenta and is present in breast milk. Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

Metabolism: It is metabolised in the liver. 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 tissue damage.

Elimination: It is excreted in the urine, mainly as the glucuronide and sulphate conjugates. The elimination half-life varies from about 1 to 4 hours. **5.3 Preclinical Safety Data**

Pseudoephedrine Hydrochloride

The oral LD50 of Pseudoephedrine Hydrochloride is 2206mg/kg in rats and 726mg/kg in mice.

Patients experiencing an overdose of Pseudoephedrine Hydrochloride may present with giddiness, headache, nausea, vomiting, sweating, thirst, tachycardia, precordial pain, palpitations, difficulty urinating, muscle weakness, muscle tension, anxiety, restlessness, insomnia, toxic psychosis, cardiac arrhythmias, circulatory collapse, convulsions, coma, and respiratory failure. Treat overdose with symptomatic and supportive treatment including removal of unabsorbed drug.

Chlorpheniramine Maleate

Oral LD50 (rat): 306 mg/kg; Oral LD50 (mice): 130 mg/kg; Oral LD50 (guinea pig): 198 mg/kg [Registry of Toxic Effects of Chemical Substances. Ed. D. Sweet, US Dept. of Health & Human Services: Cincinatti, 2010.] Also, a mild reproductive toxin to women of childbearing age.

Paracetamol

LD50 = 338 mg/kg (oral, mouse); LD50 = 1944 mg/kg (oral, rat)

Overdose and liver toxicity

Paracetamol overdose may be manifested by renal tubular necrosis, hypoglycemic coma, and thrombocytopenia. Sometimes, liver necrosis can occur as well as liver failure. Death and the requirement of a liver transplant may also occur. Metabolism by the CYP2E1 pathway releases a toxic Paracetamol metabolite known as N-acetyl-pbenzoquinoneimine (NAPQI). The toxic effects caused by this drug are attributed to NAPQI, not Paracetamol alone.

Carcinogenesis

Long-term studies in mice and rats have been completed by the National Toxicology Program to study the carcinogenic risk of Paracetamol. In 2-year feeding studies, F344/N rats and B6C3F1 mice consumed a diet containing Paracetamol up to 6,000 ppm. Female rats showed evidence of carcinogenic activity demonstrated by a higher incidence of mononuclear cell leukemia at doses 0.8 times the maximum human daily dose (MHDD). No evidence of carcinogenesis in male rats (0.7 times) or mice (1.2 to 1.4 times the MHDD) was noted. The clinical relevance of this finding in humans is unknown.

Mutagenesis

Paracetamol was not found to be mutagenic in the bacterial reverse mutation assay (Ames test). Despite this finding, Paracetamol tested positive in the in vitro mouse lymphoma assay as well as the in vitro chromosomal aberration assay using human lymphocytes. In published studies, Paracetamol has been reported to be clastogenic (disrupting chromosomes) when given a high dose of 1,500 mg/kg/day to the rat model (3.6 times the MHDD). No clastogenicity was observed at a dose of 750 mg/kg/day (1.8 times the MHDD), indicating that this drug has a threshold before it may cause mutagenesis. The clinical relevance of this finding in humans is unknown.

Impairment of Fertility

In studies conducted by the National Toxicology Program, fertility assessments have been performed in Swiss mice in a continuous breeding study. No effects on fertility were seen.

Use in pregnancy and nursing

The FDA label for Paracetamol considers it a pregnancy category C drug, meaning this drug has demonstrated adverse effects in animal studies. No human clinical studies in pregnancy have been done to this date for intravenous

Paracetamol. Use Paracetamol only when necessary, during pregnancy. Epidemiological data on oral Paracetamol use in pregnant women demonstrate no increase in the risk of major congenital malformations. Label While prospective clinical studies examining the results of nursing with Paracetamol use have not been conducted, Paracetamol is found secreted in human milk at low concentrations after oral administration. Data from more than 15 nursing mothers taking Paracetamol was obtained, and the calculated daily dose of Paracetamol that reaches the infant is about 1 to 2% of the maternal dose.

Caution should be observed when Paracetamol is taken by a nursing woman.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

- Purified Talc
- Maize starch
- Magnesium Stearate.

6.2 Incompatibilities

No Incompatibilities.

6.3 Shelf Life

36 months

6.4 Special precaution for storage

Store in a dry place below 30^0C. Protect from light.

6.5 Nature and contents of container

Coldril Capsules is blister-packed in 2 x 10's in 12 inner boxes together with paper literature inserts. The 12 inner boxes are then packed in 1 outer box.

6.6 Special precautions for disposal and other handling

- Do not throw away any medicines you no longer use.
- Ask your pharmacist or medical facility how to properly dispose of any medicine you no longer use. These measures will help protect the environment.

7. MARKETING AUTHORIZATION HOLDER & MANUFACTURING SITE ADDRESSES

Marketing Authorization Holder (MAH)

Name: Shelys Pharmaceuticals Ltd

Address: Plot No. 696, New Bagamoyo Road, Mwenge, Dar Es Salaam
P.O. BOX 32781 Dar Es Salaam

Country: Tanzania

Telephone: +255 22 2771715/6/7

E-Mail: info@tz.aspenpharma.com

Manufacturing Site Addresses

Name: Beta Healthcare International Ltd

Address: Plot No. Nairobi/Block59/135, Mogadishu Road, Off Lunga Lunga Road, Industrial Area, Nairobi

P.O. BOX 42569-00100 GPO Nairobi

Country: Kenya

Telephone: +254-20-2652042/89

E-Mail: regulatory@ke.aspenpharma.com

8. MARKETING AUTHORISATION NUMBER

See table below

9. DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISRATION

Date of First Registration: **See table below**

Date of Renewal of Registration: **See table below**

Country	Authorization no	Date of First Reg	Date of Last Renewal
DR Congo	MS.1253/10/05/DGM/0162/2016	1 Mar 2016	3 Aug 2022
Kenya	H2005/16067/187	1 Jun 2005	-
Malawi	PMPB/PL143/42	01 Jun 2005	-
Mozambique	598	2 May 2017	3 May 2022
Rwanda	Rwanda FDA-HMP-MA-0661	10 Dec 2023	-
Tanzania	TAN 22 HM 0030	1 -Jan 2022	-
Uganda	NDA/MAL/HDP/6633	01 Aug 2010	31 August 2024
Zambia	134/056	TBC	31 Dec 2024

10. DATE OF REVISION OF THE TEXT

January 2025

11. DOSIMETRY

Not applicable

12. INSTRUCTION FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable