CLEAN PROPOSED PROFESSIONAL INFORMATION FOR

CORYX

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

CORYX Effervescent tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each effervescent tablet contains:

Chlorpheniramine maleate	4 mg
Pseudoephedrine hydrochloride	50 mg
Aspirin	600 mg
Vitamin C (ascorbic acid)	330 mg

Contains sweetener: aspartame 53 mg per tablet

For full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Effervescent tablets.

Round, biplane, beige to light yellow-coloured effervescent tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CORYX is indicated in adults and children over 16 years for the treatment of symptoms associated with colds and influenza.

4.2 Posology and method of administration

Posology

Use the lowest effective dose for the shortest possible duration of treatment.

Adults and children over 16 years

One tablet every 8 hours if necessary.

Gastric irritation may be reduced by taking doses after food.

Children under 16 years

CORYX is contraindicated in children under the age of 16 years (see **section 4.3**).

Method of administration

Place one tablet in a glass of warm (or cold if so wished) water and allow to dissolve. Drink all the contents immediately once the whole tablet has dissolved (see **section 6.6**).

4.3 Contraindications

CORYX is contraindicated in:

- patients with known hypersensitivity to chlorpheniramine, pseudoephedrine, aspirin (or any other NSAID) or vitamin C (ascorbic acid), or to any of the excipients in CORYX (see **section 6.1**).

- patients with coronary disease, hypertension, cardiovascular disease, heart failure, hyperthyroidism, epilepsy.
- pregnancy and breastfeeding (see **section 4.6**).
- patients being treated with monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping such treatment (see **section 4.5**).
- patients with a history of gastrointestinal perforation, ulceration or bleeding (PUBs) related to previous nonsteroidal anti-inflammatory medicines (NSAIDs) including aspirin, as contained in CORYX.
- patients with haemophilia, severe renal impairment and patients receiving oral anticoagulant therapy (see **section 4.5**).
- patients with active or history of recurrent ulcer / haemorrhage / perforations.
- patients with phenylketonuria (see **section 4.4**).
- children under the age of 16 years (see **section 4.4**).
- patients with severe hypertension or uncontrolled hypertension.
- patients with severe acute or chronic kidney disease/renal failure.

4.4 Special warnings and precautions for use

CORYX may predispose to cardiovascular events, gastrointestinal events, or cutaneous reactions which may be fatal.

Do not use for more than 10 days without consulting your doctor.

Prolonged use of high doses may lead to anaemia, blood dyscrasias, gastrointestinal haemorrhage, peptic ulceration and renal papillary necrosis.

Kidney or liver impairment

Patients suffering from kidney or liver disease should take CORYX under medical supervision. Care should be taken in patients with urinary retention. CORYX is contraindicated in patients with severe acute or chronic kidney disease/renal failure (see **section 4.3**).

Sensitivity to aspirin

CORYX contains aspirin, therefore it should be used with caution in patients with asthma or allergic disorders. It should not be given to patients with a history of nasal polyps associated with aspirin or sensitivity reactions to aspirin or other NSAIDs (see **section 4.3**).

Drowsiness

The use of this medicine may lead to drowsiness and impaired concentration, which may be aggravated by the simultaneous intake of alcohol or other central nervous system depressants. Patients should be advised, particularly at the initiation of therapy, against taking charge of vehicles or machinery or performing potentially hazardous tasks where loss of concentration could lead to accidents (see **section 4.7**).

Reye's syndrome

Aspirin has been implicated in Reye's syndrome, a rare but serious illness in children and teenagers who have or are recovering from chicken pox and influenza. A medical practitioner should be consulted before giving CORYX to children under 16 years of age; therefore CORYX is contraindicated in children under 16 years of age

and in teenagers with chickenpox and influenza. A doctor should be consulted before CORYX is used in such patients (see **section 4.3**).

Cardiovascular disease

There appears to be a higher risk of cardiovascular events with higher doses and longer duration of treatment.

Due to inhibition of prostaglandin synthesis, fluid retention and oedema have been observed in patients taking aspirin, which is contained in CORYX; therefore CORYX should be used with caution in patients with compromised cardiac function and other conditions predisposing to, or worsened by, fluid retention. Patients with pre-existing congestive heart failure or hypertension should not take CORYX (see **section 4.3**).

CORYX should be used with caution in patients with cardiovascular disease such as ischaemic heart disease, dysrhythmia or tachycardia, and occlusive vascular disorders, including arteriosclerosis or aneurysms. Anginal pains may be precipitated in patients with angina pectoris.

Other

CORYX should be used with caution in patients with diabetes mellitus, closed-angle glaucoma and prostatic hyperplasia.

Elderly

The elderly have an increased frequency of adverse reactions to NSAIDs, such as aspirin in CORYX, especially gastrointestinal perforation, ulceration and bleeding (PUBs) which may be fatal.

Gastrointestinal disease

The risk of gastrointestinal perforation, ulceration or bleeding (PUBs) is higher with increasing doses of CORYX, in patients with a history of ulcers, and the elderly.

When gastrointestinal bleeding or ulceration occurs in patients receiving CORYX, treatment with CORYX should be stopped.

CORYX should be given with caution to patients with a history of gastrointestinal disease (e.g. ulcerative colitis, Crohn's disease, hiatus hernia, gastro-oesophageal reflux disease, angiodysplasia) as the condition may be exacerbated (see **section 4.3**).

Care should be taken in patients with pyloroduodenal obstruction.

Surgery

CORYX contains aspirin that may increase blood loss during surgery. A neuraxial regional anaesthetic technique is not recommended for a patient taking CORYX in combination with other medicines with anti-coagulant effects.

Skin reactions

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported. CORYX should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Pregnancy

Regular use of NSAIDs, such as aspirin in CORYX, during the third trimester of pregnancy, may result in premature closure of the foetal ductus arteriosus *in utero*,

and in persistent pulmonary hypertension of the new-born. The onset of labour may be delayed and its duration increased. CORYX is contraindicated in pregnancy (see **section 4.3**).

Laboratory tests

CORYX contains aspirin, therefore it can interfere with thyroid function tests.

Skin testing

CORYX may suppress the cutaneous histamine response to allergen extracts and should be stopped several days before skin testing (see **section 4.5**).

Hyperoxaluria

CORYX should be given with care to patients with hyperoxaluria. Tolerance may be induced with prolonged use of large doses of vitamin C (ascorbic acid).

Hypokalaemia and renal tubular acidosis (RTA)

Severe hypokalaemia and renal tubular acidosis (RTA) have been reported due to prolonged use of NSAIDs at higher than recommended doses. CORYX-induced renal tubular acidosis should therefore be considered in patients with unexplained hypokalaemia and metabolic acidosis.

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 (see section 4.8). The risk is increased in patients with severe or

uncontrolled hypertension, or with severe acute or chronic kidney disease/renal failure (see section 4.3).

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.

Aspartame

CORYX contains 53 mg aspartame in each tablet. Aspartame is a source of phenylalanine. CORYX is contraindicated in patients with phenylketonuria (see **section 4.3**).

4.5 Interactions with other medicines and other forms of interaction

CORYX may enhance the sedative effects of central nervous system (CNS) depressants including alcohol, barbiturates, hypnotics, opioid / narcotic analgesics, anxiolytic sedatives, tranquillisers and antipsychotics.

CORYX has an additive antimuscarinic action with other antimuscarinic medicines, such as atropine and some antidepressants (both tricyclics and MAOIs). Care should therefore be observed when tricyclic antidepressants, reserpine, methyldopa or atropine are taken concomitantly.

CORYX may cause a hypertensive crisis in patients receiving a MAOI [including a reversible monoamine oxidase inhibitor (RIMA)] (see **section 4.3**).

CORYX should be avoided or used with care in patients undergoing anaesthesia with volatile or halogenated anaesthetics as they may induce ventricular fibrillation. An increased risk of dysrhythmias may occur if given to patients receiving digoxin, quinidine or tricyclic antidepressants and there is an increased risk of vasoconstrictor or pressor effects in patients receiving ergot alkaloids or oxytocin.

Use of two or more NSAIDs, including aspirin as in CORYX, concomitantly could result in an increase in side effects.

Use of corticosteroids concomitantly may result in an increased risk of gastrointestinal perforation, ulceration or bleeding (PUBs).

Some of the effects of aspirin on the gastrointestinal tract are enhanced by alcohol.

CORYX may enhance the activity of warfarin and oral antidiabetic preparations and sulphonamides.

Use of anti-platelet medicines and selective serotonin reuptake inhibitors (SSRIs) concomitantly may result in increased risk of gastrointestinal bleeding.

CORYX diminishes the effects of anti-gout preparations such as probenecid and sulphinpyrazone.

Barbiturates and other sedatives may mask the respiratory symptoms of aspirin overdosage and have been reported to enhance its toxicity.

CORYX could mask the warning signs of damage caused by ototoxic medicines such as aminoglycoside antibiotics.

CORYX may suppress the cutaneous histamine response to allergen extracts and should be stopped several days before skin testing (see **section 4.4**).

CORYX should be used with caution with dipyridamole, metoclopramide, metoprolol, carbonic anhydrase inhibitors, corticosteroids, antacids and adsorbents (including aluminium hydroxide and kaolin), gold compounds, sulfonylurea hypoglycaemic medicines, zafirlukast, methotrexate, phenytoin, valproate, mifepristone, calcium channel blockers, such as verapamil, and spironolactone.

4.6 Fertility, pregnancy and lactation

Pregnancy

CORYX is contraindicated in pregnancy (see **sections 4.3** and **4.4**).

Use of NSAIDs, such as CORYX, around 20 weeks of gestation or later in pregnancy may cause a rare but serious foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment.
Complications of prolonged oligohydramnios include limb contractures and delayed lung maturation, which may require invasive procedures such as exchange transfusion or dialysis, in some cases.

Breastfeeding

CORYX is contraindicated in breastfeeding (see **section 4.3**).

CORYX contains pseudoephedrine, which is excreted in breast milk.

4.7 Effects on ability to drive and use machines

CORYX may cause drowsiness or sleepiness which may interfere with the patient's ability to drive or operate machines.

Because CORYX may produce sedation, patients should not operate machinery, drive cars, climb dangerous heights or perform potentially dangerous tasks where impaired decision making could lead to accidents.

4.8 Undesirable effects

Tabulated summary of adverse reactions

Blood and the lymphatic system disorders

Less frequent:	Agranulocytosis, thrombocytopenia, pancytopenia, aplastic anaemia, iron-deficiency anaemia (during long-term salicylate therapy), leukopenia, haemolytic anaemia.
Frequency unknown:	Increased bleeding time, decreased platelet adhesiveness, hypoprothrombinaemia, haemolysis (in patients with G6PD deficiency).

Immune system disorders

Frequency unknown:	Hypersensitivity reactions, including urticaria, skin eruptions, angioedema, rhinitis and severe, even fatal, paroxysmal bronchospasm and dyspnoea (especially in asthmatics, chronic urticaria or rhinitis), anaphylaxis.

Metabolism and nutrition disorders

Frequency unknown: Altered metabolism, including disturbances of glucose metabolism, hypokalaemia (reported post-marketing following prolonged use of NSAIDs at higher than recommended doses).

Psychiatric disorders

Frequent: Anxiety, restlessness, insomnia.

Less frequent: Hallucinations (particularly in children).

Frequency unknown: Sleep disturbances, confusion, fear, irritability, psychotic states, euphoria, nervousness.

Nervous system disorders

Frequent: Central nervous system depression, ranging from slight drowsiness to deep sleep, including lassitude, dizziness, or incoordination, headache, psychomotor impairment, antimuscarinic effects, such as dry mouth, thickened respiratory tract secretions, blurred vision, urinary difficulty or retention, constipation and increased gastric reflux.

Less frequent: Paradoxical stimulation (especially at high doses, in children and the elderly).

Frequency unknown: Facial dyskinesia, adverse mental effects (particularly in children), convulsions, paraesthesias, extrapyramidal effects, tremor, depression, tingling, heaviness and

weakness of the hands, posterior reversible encephalopathy syndrome (PRES) (see **section 4.4**), Reversible cerebral vasoconstriction syndrome (RCVS) (see **section 4.4**).

Eye disorders

Frequency unknown: Blurred vision, diplopia.

Ear and labyrinth disorders

Frequency unknown: Tinnitus, hearing loss.

Cardiac disorders

Frequent: Tachycardia.

Less frequent: Palpitations, cardiac dysrhythmias.

Frequency unknown: Bradycardia, anginal pain, cardiac arrest, oedema, cardiac failure.

Vascular disorders

Frequency unknown: Hypotension, with dizziness, fainting and flushing, vasoconstriction, hypertension, cerebral haemorrhage, pulmonary oedema.

Respiratory, thoracic and mediastinal disorders

Frequency unknown: Impaired sense of smell, dryness of the respiratory passages, tightness of the chest, dyspnoea.

Gastrointestinal disorders

Frequent:	Gastrointestinal disturbances, nausea, dyspepsia, vomiting.
Less frequent:	Major upper gastrointestinal bleeding, diarrhoea, epigastric pain.
Frequency unknown:	Irritation of the gastric mucosa with erosion, ulceration, haematemesis and melaena, impaired sense of taste, ischaemic colitis, loss of appetite, epigastric distress, constipation, dryness of the mouth and throat, hypersalivation, peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal, flatulence, abdominal pain, ulcerative stomatitis, exacerbation of colitis and Crohn's disease, gastritis.

Hepatobiliary disorders

Frequency unknown:	Hepatotoxicity, hepatic injury, elevation of aminotransferase values.

Skin and subcutaneous tissue disorders

Less frequent:	Skin rashes, fixed medicine eruptions.
Frequency unknown:	Exfoliative dermatitis, sweating, hair loss, bullous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Musculoskeletal, connective tissue and bone disorders

Frequency unknown: Myalgia.

Renal and urinary disorders

Less frequent: Urinary retention, analgesic nephropathy.

Frequency unknown: Hyperoxaluria, renal calcium oxalate calculi, renal impairment, difficulty in micturition, urinary frequency and dysuria, renal tubular acidosis (reported post-marketing following prolonged use of NSAIDs at higher than recommended doses).

General disorders and administrative site conditions

Frequency unknown: Weakness, fatigue.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website or to Cipla Medpro (Pty) Ltd by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

CORYX overdosage may result in convulsions and hypertension in susceptible patients. Overdosage may also cause tachycardia, dysrhythmias and anginal pain,

nausea, dizziness, hyperventilation, respiratory alkalosis, metabolic acidosis, hypoglycaemia, vomiting, irritation of gastric mucosa with dyspepsia, haematemesis and melaena.

Overdosage with sedating antihistamines, such as chlorpheniramine in CORYX, is associated with antimuscarinic, extrapyramidal and CNS effects.

When CNS stimulation predominates over CNS depression, which is more likely in children or the elderly, it causes ataxia, excitement, tremors, psychoses, hallucinations and convulsions; hyperpyrexia may also occur. Deepening coma and cardiorespiratory collapse may follow.

In adults, CNS depression is more common with drowsiness, coma and convulsions, progressing to respiratory failure and cardiovascular collapse.

Prolonged use at higher than recommended doses may result in severe hypokalaemia and renal tubular acidosis. Symptoms may include reduced level of consciousness and generalised weakness (see **section 4.4** and **section 4.8**).

The patient must be taken to a doctor or hospital immediately as specialised treatment may be necessary. Treatment is supportive and symptomatic, the serum salicylate levels should be closely monitored and forced alkaline diuresis instituted if appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 5.8. Preparations for the common cold including nasal decongestants.

Pharmacodynamic effects

CORYX has analgesic, antipyretic, antihistaminic and decongestant properties.

Chlorpheniramine maleate is a potent antihistamine (H1-antagonist) that causes a moderate degree of sedation; it also has antimuscarinic activity. It is a common ingredient of compound preparations for symptomatic treatment of coughs and the common cold.

Pseudoephedrine is a direct and indirect acting sympathomimetic. It is given orally for the symptomatic relief of nasal congestion and is commonly combined with other ingredients in preparations intended for the relief of cough and cold symptoms.

Aspirin is a salicylate nonsteroidal anti-inflammatory medicine (NSAID). It has analgesic, anti-inflammatory and antipyretic properties and acts as an inhibitor of the enzyme cyclo-oxygenase, which results in the direct inhibition of the biosynthesis of prostaglandins and thromboxanes from arachidonic acid. Aspirin also inhibits platelet aggregation. It is used for the relief of mild to moderate pain and minor febrile conditions, such as colds or influenza.

Vitamin C (ascorbic acid) contributes to the normal function of the immune system and is an antioxidant for the maintenance of good health.

5.2 Pharmacokinetic properties

Chlorpheniramine maleate

Absorption

Chlorpheniramine maleate is absorbed relatively slowly from the gastrointestinal tract and peak plasma concentrations occur about 2,5 to 6 hours after oral doses. Bioavailability is low, values of 25 to 50 % have been reported.

Chlorpheniramine appears to undergo considerable first-pass metabolism.

A duration of action of 4 to 6 hours has been reported; this is shorter than may be predicted from pharmacokinetic parameters.

Distribution

About 70 % of chlorpheniramine in the circulation is bound to plasma proteins. Chlorpheniramine is widely distributed in the body and enters the CNS.

Biotransformation

Chlorpheniramine maleate is extensively metabolised. Metabolites include desmethyl- and didesmethylchlorphenamine.

Elimination

There is wide interindividual variation in the pharmacokinetics of chlorpheniramine; values ranging from 2 to 43 hours have been reported for the half-life.

Unchanged chlorpheniramine and metabolites are excreted mainly in the urine; excretion is dependent on urinary pH and flow rate. Only trace amounts have been found in the faeces.

Paediatric population

In children, more rapid and extensive absorption, faster clearance and a shorter half-life have been reported.

Pseudoephedrine

Absorption

Pseudoephedrine is readily absorbed from the gastrointestinal tract.

Distribution

Small amounts of pseudoephedrine are distributed into breast milk.

Biotransformation and elimination

Pseudoephedrine is excreted largely unchanged in the urine with small amounts of its hepatic metabolite.

It has a half-life of about 5 to 8 hours. Elimination is enhanced, and the half-life accordingly shortened, in acidic urine.

Aspirin

Absorption

When taken orally, the T_{max} is 1 hour. Absorption of non-ionised aspirin occurs in the stomach and intestine. Some aspirin is hydrolysed to salicylate in the gut wall. Once absorbed, aspirin is rapidly converted to salicylate, but during the first 20 minutes after an oral dose, aspirin is the main form of the medicine in the plasma.

Distribution

Aspirin is 80 to 90 % bound to plasma proteins and is widely distributed; its volume of distribution is reported to be 170 mL/kg in adults. As plasma-medicine concentrations increase, the binding sites on the proteins become saturated and the

volume of distribution increases. Both aspirin and salicylate have pharmacological activity although only aspirin has an anti-platelet effect. Salicylate is extensively bound to plasma proteins and is rapidly distributed to all body parts. Salicylate appears in breast milk and crosses the placenta.

Biotransformation

Salicylate is mainly eliminated by hepatic metabolism; the metabolites include salicyluric acid, salicyl phenolic glucuronide, salicylic acyl glucuronide, gentisic acid and gentisuric acid. The formation of the major metabolites, salicyluric acid and salicyl phenolic glucuronide, is easily saturated and follows Michaelis-Menten kinetics; the other metabolic routes are first-order processes. As a result, steady-state plasma-salicylate concentrations increase disproportionately with dose.

Elimination

After a 325 mg aspirin dose, elimination is a first-order process and the plasma-salicylate half-life is about 2 to 3 hours; at high aspirin doses, the half-life increases to 15 to 30 hours. Salicylate is also excreted unchanged in the urine; the amount excreted by this route increases with increasing dose and also depends on urinary pH. About 30 % of a dose is excreted in alkaline urine, compared with 2 % of a dose in acidic urine. Renal excretion involves glomerular filtration, active renal tubular secretion and passive tubular reabsorption. Salicylate is removed by haemodialysis.

Vitamin C

Absorption

Ascorbic acid is readily absorbed from the gastrointestinal tract and is widely distributed in the body tissues. Plasma concentrations of ascorbic acid rise as the dose ingested is increased, until a plateau is reached with doses of about 90 to 150 mg daily.

Distribution

Body stores of ascorbic acid in healthy persons are about 1,5 g although more may be stored at intakes above 200 mg daily. The concentration is higher in leucocytes and platelets than in erythrocytes and plasma. In deficiency states the concentration in leucocytes declines later and at a slower rate, and has been considered to be a better criterion for the evaluation of deficiency than the concentration in plasma. Ascorbic acid crosses the placenta and is distributed into breast milk.

Biotransformation

Ascorbic acid is reversibly oxidised to dehydroascorbic acid; some is metabolised to ascorbate-2-sulfate, which is inactive, and oxalic acid which are excreted in the urine.

Elimination

Ascorbic acid in excess of the body's needs is rapidly eliminated unchanged in the urine; this generally occurs with intakes exceeding 100 mg daily. Ascorbic acid is removed by haemodialysis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Adipic acid

Aspartame

Beta-carotene 1 % CWS

Citric acid anhydrous

Colloidal silicon dioxide

Macrogol 6000

Pineapple flavour 76136-31

Sodium bicarbonate

Sodium carbonate anhydrous

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

12 months.

6.4 Special precautions for storage

Store in the tube, tightly closed at or below 25 °C.

Protect from light and moisture.

Keep in the original container until ready for use.

6.5 Nature and contents of container

Effervescent tablets packed in an aluminium tube with a white plastic closure, packed in a printed carton box. Each tube contains 12 tablets. Each carton contains one tube (12’s).

6.6 Special precautions for disposal and other handling

CORYX effervescent tablets produce a light yellow solution with a pineapple flavour once dissolved in ± 200 mL of water.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9, Parc du Cap,

Mispel Street,

Bellville,

7530, RSA

Customer care: 080 2226662

8. REGISTRATION NUMBER

27/5.8/0435

Namibia: NS1 04/17.5.8/1514
Botswana: S3 BOT0801262

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18 May 1993

10. DATE OF REVISION OF THE TEXT

06 November 2024