Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

CONTUS-650 TABLETS (Chlorphenamine Phenylephrine and Paracetamol Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains:

Chlorphenamine Maleate BP.....2 mg

Phenylephrine Hydrochloride BP .....5 mg

Paracetamol BP.....650 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pale Orange coloured bolus shaped uncoated tablets with a central scoring on one side and plain on the reverse side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

CONTUS-650 Tablets are indicated for the treatment of the symptoms associated with Influenza, cold and sinusitis. It is also indicated for the treatment of pain, fever, runny nose, sneezing and nasal congestion associated with the common cold.

4.2 Posology and Method of Administration

Adults: One tablet to be taken 3-4 times daily or as directed by the Physician.

4.3 Contraindications

Hypersensitivity to any of the ingredients. Because of its drying effect on lower respiratory secretions, Chlorphenamine Maleate; Phenylephrine HCl is not recommended in the treatment of bronchial asthma. The product is also contraindicated in patients with severe hypertension, severe coronary artery disease, narrow-angle glaucoma, urinary retention, peptic ulcer, and in patients on MAO inhibitor therapy.
Hypersensitivity to Phenylephrine or any component of the formulation; hypertension; ventricular tachycardia.

Phenylephrine is contraindicated in patients with hypertension or with peripheral vascular insufficiency (ischemia may result with risk of gangrene

or thrombosis of compromised vascular beds). Phenylephrine should not be used in patients known to be hypersensitive to the drug or in those receiving a monoamine oxidase inhibitor (MAOI).
Use with or within 14 days of MAO inhibitor therapy. Paracetamol should be given with care to patients taking other drugs that affect the liver.

4.4 Special Warnings and Precautions for Use

Because of its antihistamine component, Chlorphenamine Maleate; Contus should be used with caution in patients with a history of bronchial asthma, gastrointestinal obstruction, or urinary bladder neck obstruction.
Because of its sympathomimetic component, Phenylephrine Hydrochloride, Contus should be used judiciously and sparingly in patients with hypertension, diabetes, heart disease, increased intraocular pressure, hyperthyroidism, or prostatic
Hypertrophy. Sympathomimetics may produce central nervous system stimulation with convulsions or cardiovascular collapse with accompanying hypotension. Use with caution in patients with asthma, bowel obstruction/narrowing, hyperthyroidism, diabetes mellitus, cardiovascular disease, ischemic heart disease, increased intraocular pressure, prostatic hyperplasia or in the elderly. When used for self-medication (OTC), notify healthcare provider if symptoms do not improve within 7 days or are accompanied by fever. Discontinue and contact healthcare provider if nervousness, dizziness, or sleeplessness occur. Not for OTC use in children <2 years of age. Antihistamines may produce drowsiness or excitation, particularly in children and elderly patients. Do not exceed recommended dosage. Especially in infants and small children, antihistamines in overdosage may cause hallucinations, convulsions, and death. Because Phenylephrine is an adrenergic agent, it should be given with caution to patients with thyroid diseases, diabetes mellitus and heart diseases or those receiving tricyclic antidepressants. Men with symptomatic, benign prostatic hypertrophy can experience urinary retention when given oral nasal decongestants. Phenylephrine can cause a decrease in cardiac output, and extreme caution should be used when administering the drug parenterally or orally to patients with arteriosclerosis, to elderly individuals, and/or to patients with initially poor cerebral or coronary circulation. Phenylephrine should be used with caution in patients with cardiovascular disease. Caution is to be exercised when driving, operating machinery, or performing other hazardous activities.
Acetaminophen/Chlorphenamine/Phenylephrine may cause dizziness or drowsiness. If patient experiences dizziness or drowsiness, these activities are to be avoided. Alcohol is to be used with caution. Alcohol may increase drowsiness and dizziness while taking Acetaminophen / Chlorphenamine / Phenylephrine. Alcohol and Acetaminophen together may also be damaging to the liver.

Excipients warnings:

Parahydroxybenzoate and their esters: The medicinal product contains Sodium methyl parahydroxybenzoate and Sodium propyl parahydroxybenzoate. May cause allergic reactions (possibly delayed).

This medicinal product contains colouring agent with approved generally recognized as safe (GRAS)- FEMA- JEFCA ingredients.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction Chlorphenamine can cause potentially negative interactions when combined with any of the following drugs:
Acetylcholinesterase Inhibitor Medications: Taking Chlorphenamine with an acetylcholinesterase inhibitor can make both medications less effective.
Anticholinergic Drugs: Combining an anticholinergic medication with Chlorphenamine (which has anticholinergic effects) can increase the risk of Chlorphenamine side effects, such as dry eyes or difficulty passing urine.
Monoamine Oxidase Inhibitors (MAOIs**):** Taking Chlorphenamine and an MAOI together can prolong and intensify certain side effects of Chlorphenamine (such as drowsiness, dry eyes, or difficulty passing urine).
Other Medications That Cause Drowsiness**:** combining Chlorphenamine with any other medication that also causes drowsiness, as undesirable side effects (such as excessive drowsiness, dizziness, or confusion).
Phenothiazines**:** Chlorphenamine may increase the risk of a dangerous irregular heart rhythm (arrhythmia) due to a phenothiazine medication. In addition, combining Chlorphenamine with a phenothiazine increases the risk of excessive drowsiness.

Pramlintide: Both pramlintide and anticholinergic medications (including Chlorphenamine) can slow down the movement of food through the digestive tract. Taking them together can increase the risk of constipation or nausea.

Phenylephrine Hydrochloride:

The co administration of Monoamine Oxidase Inhibitors (MAOIs) or tricyclic antidepressants and an indirect or mixed-acting sympathomimetic may result in a hypertensive crisis. Direct-acting sympathomimetics appear to interact minimally, if at all such concomitant use is clearly identified as a contra-indication on the labelling of all Phenylephrine-containing products and the appropriate warnings are provided. Additionally sympathomimetics may reduce the efficacy of beta-blocking and anti-hypertensive drugs. Conditions where these drugs are used are contra-indicated for the product.

Drug	Effect
Phenylephrine with prior administration of monoamine oxidase inhibitors (MAOI).	Cardiac pressor response potentiated. May cause acute hypertensive crisis.
Phenylephrine with tricyclic antidepressants.	Pressor response increased.
Phenylephrine with ergot alkaloids.	Excessive rise in blood pressure.
Phenylephrine with bronchodilator sympathomimetic agents and with epinephrine or other sympathomimetics.	Tachycardia or other arrhythmias may occur.
Phenylephrine with prior administration of propranolol or other β-adrenergic blockers.	Cardiostimulating effects blocked.
Phenylephrine with atropine sulfate.	Reflex bradycardia blocked; pressor response enhanced.
Phenylephrine with prior administration of phentolamine or other α-adrenergic blockers.	Pressor response decreased.
Phenylephrine with diet preparations, such as amphetamines or phenylpropanolamine.	Synergistic adrenergic response.

Paracetamol should be given with care to patients taking other drugs that affect the liver. The speed of absorption of paracetamol may be increased by metoclopramide or domperidone. Concurrent use need not be avoided. The absorption of paracetamol may possibly be reduced if cholestyramine is given at the same time, but the reduction in absorption is small if given an hour later. The anticoagulatory effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding.

4.6 Pregnancy and Lactation

Pregnancy:

Animal reproduction studies have not been conducted with Contus-650 Tablets. It is not known whether this product can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity.

Studies with chlorpheniramine maleate in rabbits and rats at doses up to 50 times and 85 times the human dose, respectively, revealed no evidence of harm to the fetus. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Contus-650 Tablets should be used during pregnancy only if clearly needed.

Lactation:

It is not known whether all the ingredients in Contus-650 Tablets – chlorpheniramine maleate, Phenylephrine HCl & paracetamol are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from this product, a decision should be made whether to discontinue the drug, taking into account the importance of the drug to the mother.

Based on information from related drugs, Chlorphenamine maleate may pass into breast milk. Use is not recommended because of the risk of adverse effects, such as unusual excitement or irritability, especially in infants. Phenylephrine may pass into breast milk and affect a nursing baby. Hence it is not advisable to use this medication without first consulting doctor. Paracetamol is excreted into milk in small amounts. Though it is considered safe in breast feeding, a single case of maculopapular rash in nursing infant has been reported.

4.7 Effects on Ability to Drive and Use Machines

CONTUS-650 Tablets will produce drowsiness. So avoid driving a motor vehicle or operating machinery under this medication

4.8 Undesirable Effects

Contus-650 Tablets are generally well tolerated when taken in prescribed dosage.

Chlorphenamine:

Slight to moderate drowsiness may occur and is the most frequent side effect. Other possible side effects of antihistamines in general include: Urticaria, drug rash, anaphylactic shock, photosensitivity, excessive perspiration, chills, and dryness of the mouth, nose and throat.

Cardiovascular:
Hypotension, headache, palpitation, tachycardia, extrasystoles.
Hematological: Hemolytic anemia, thrombocytopenia, agranulocytosis

CNS:
Sedation, dizziness, disturbed coordination, fatigue, convulsion, restlessness, excitation, nervousness, tremor, irritability, insomnia, euphoria, paresthesia, blurred vision, dipilopia, vertigo, tinnitus, hysteria, neuritis, convulsion.

Gastrointestinal:
Epigastric distress, anorexia, nausea, vomiting, diarrhea, constipation.

Genitourinary:
Urinary frequency, difficult urination, urinary retention, early menses.

Respiratory:
Thickening of bronchial secretions, tightness of chest, wheezing and nasal stuffiness.

Phenylephrine Hydrochloride:

The most frequent reports involved the skin and subcutaneous tissues (59 reports) with urticaria (20 cases), face oedema (7 cases), and rash (6 cases). The other most frequent events (> 4 cases) were urinary retention (7 cases),

bronchospasm (7 cases), sedation (4 cases) and diarrhoea (4 cases). No cases of cerebrovascular accidents or myocardial infarction were reported. There were two reports of hypertension and one of aggravated hypertension.

Central Nervous System - Restlessness, anxiety, nervousness and dizziness. Cardiovascular - Hypertension
Other - Primordial pain, respiratory distress, tremor and weakness.

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

Reporting of suspected adverse reactions

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

4.9 Overdose

Chlorphenamine: Effects of chlorphenamine over dosage may vary from central nervous system depression (sedation, apnea, diminished mental alertness, cardiovascular collapse) to stimulation (insomnia, hallucinations, tremors, or convulsions) to death.
Overdose symptoms may be sedation, apnea, and cardiovascular collapse to stimulation, insomnia, hallucinations, tremors or convulsions. Also there may be dizziness, tinnitus, ataxia, blurred vision, hypotension, dry mouth, flushing and abdominal symptoms.

Treatment: Gastric lavage may be necessary using activated charcoal and saline. Hyperosmotic cathartics such as Milk of Magnesia may hasten elimination of residual cling. Vasopressors can be used to correct hypotension. Diazepam may be used to control seizures. Hyperpyrexia can be treated with cool sponges or a hypothermic blanket. It is not usually recommended to induce vomiting for a chlorphenamine overdose. Treatment may also involve supportive care, which consists of treating the symptoms that occur as a result of the overdose.

Phenylephrine: Symptoms of a Phenylephrine overdose include extreme tiredness, sweating, dizziness, a slow heartbeat, and coma. Signs and symptoms of overdosage with Phenylephrine include hypertension, headache, convulsions, cerebral hemorrhage, and vomiting. Ventricular premature beats and short paroxysms of ventricular tachycardia may also occur. Headache may be a symptom of hypertension. Bradycardia may also

be seen early in Phenylephrine overdosage through stimulation of baroreceptors. Treatment should be symptomatic.

Paracetamol: In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma and thrombocytopenia may also occur. Importantly, young children seem to be more resistant than adults to the hepatotoxic effect of an acetaminophen overdose.
Despite this, the measures outlined below should be initiated in any adult or child suspected of having ingested an acetaminophen overdose.
Early symptoms following a potentially hepatotoxic overdose may include: nausea vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Treatment: The stomach should be emptied promptly by lavage or by induction of emesis with syrup of ipecac. Patients' estimates of the quantity of a drug ingested are notoriously unreliable. Therefore, if an acetaminophen overdose is suspected, a serum acetaminophen assay should be obtained as early as possible, but no sooner than four hours following ingestion. Liver function studies should be obtained initially and repeated at 24-hour intervals. The antidote, N-acetylcysteine, should be administered as early as possible, preferably within 16 hours of the overdose ingestion for optimal results, but in any case, within 24 hours. Following recovery, there are no residual, structural or functional hepatic abnormalities.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Chlorphenamine Maleate is an alkylamine derivative, is a sedating antihistamine that causes moderate degree of sedation: it also has antimuscarinic activity**.** H1-antagonists such as chlorphenamine maleate do not prevent the release of histamine but rather compete with free histamine for binding at H1-receptor sites. These drugs competitively antagonize the effects of histamine on H1-receptors in the GI tract, uterus, large blood vessels, and bronchial smooth muscle. Blockade of H1-receptors also suppresses the formation of edema, flare, and pruritis that result from histaminic activity. H1-antagonists also possess anticholinergic properties in varying degrees. The anticholinergic activity of propylamine derivatives such as chlorphenamine is moderate. This anticholinergic action appears to be due to a central antimuscarinic effect. Sedative effects from chlorphenamine result from antagonism at central histaminergic receptors. Chronic administration may lead to some degree of tolerance.

Phenylephrine Hydrochloride is a sympathomimetic with mainly direct effects on adrenergic receptors. It has predominantly alpha adrenergic activity and is without significant stimulating effects on the CNS at the usual doses. Its pressor activity is weaker than that of noradrenalin but of

longer duration. It causes vasoconstriction of the arterioles of the nasal mucosa and conjunctiva. It is used as a decongestant for temporary relief of nasal congestion caused by hay fever, allergies, the common cold, a sinus infection, or other upper respiratory diseases. Decongestants act on the adrenergic receptors in the nasal passages and constrict (narrow) the blood vessels. This action results in relief from the stuffy feeling related to nasal congestion. Decongestant use promotes nasal and sinus drainage.
Phenylephrine is a potent postsynaptic-a-receptor agonist with little effect on ß receptors of the heart. Phenylephrine has no effect on ß-adrenergic receptors of the bronchi or peripheral blood vessels. A direct action at receptors accounts for the greater part of its effects, only a small part being due to its ability to release norepinephrine.
Therapeutic doses of phenylephrine mainly cause vasoconstriction. Phenylephrine increases resistance and, toa lesser extent, decreases capacitance of blood vessels. Total peripheral resistance is increased, resulting in increased systolic and diastolic blood pressure. Pulmonary arterial pressure is usually increased, and renal blood flow is usually decreased. Local vasoconstriction and hemostasis occur following topical application or infitration of phenylephrine into tissues.
The main effect of phenylephrine on the heart is bradycardia; it produces a positive inotropic effect on the myocardium in doses greater than those usually used therapeutically. Rarely, the drug may increase the irritability of the heart, causing arrhythmias. Cardiac output is decreased slightly. Phenylephrine increases the work of the heart by increasing peripheral arterial resistance. Phenylephrine has a mild central stimulant effect.

Paracetamol acts by inhibiting cyclooxygenase enzyme in brain, thus inhibiting the formation of prostaglandins. It is a poor inhibitor of prostaglandin sysnthesis in peripheral tissues.
Analgesic: The mechanism of analgesic action has not been fully determined. Acetaminophen produces analgesia by elevation of the pain threshold and antipyresis through action on the hypothalamic heat regulating center 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 on the hypothalamic Heat regulating centre to produce peripheral vasodilation resulting in increased blood Flow through the skin, sweating and heat loss. The central action probably involves inhibition of prostaglandin synthesis in the hypothalamus

5.2 Pharmacokinetic Properties
Pharmacokinetics of Chlorphenamine Maleate
Absorption
Chlorpheniramine may be administered orally, subcutaneously, intravenously, or intramuscularly. Chlorpheniramine is well absorbed from the GI tract. Food delays absorption; however, bioavailability is not affected.

Distribution and metabolism

Onset of action of chlorpheniramine regular-release formulations is about 30—60 minutes, with Cmax occurring in about 2 hours and maximum therapeutic effect in about 6 hours. The duration of action is between 4—8 hours. Protein binding is approximately 72%. Chlorpheniramine is widely distributed in body tissues and fluids, and it crosses the placenta and is excreted into breast milk.
Metabolism of chlorpheniramine is extensive and rapid, first occurring in the gastric mucosa and then on first-pass through the liver, which may be saturable. N-dealkylation produces several metabolites, which are excreted in the urine along with the parent compound. Plasma half-life is between 2—4 hours, but the terminal elimination half-life varies with age. The half-life in healthy adults and children is 20—24 hours and 10—13 hours, respectively. In chronic renal failure patients undergoing haemodialysis, the half-life may be as long as 280—330 hours.

Elimination

Excretion rates are dependent on the pH of urine and urinary flow, with the rate decreasing as the pH rises and urinary flow decreases.

Pharmacokinetics of Phenylephrine hydrochloride:

Absorption

Phenylephrine is readily and completely absorbed from the gastro-intestinal tract after oral administration. Following oral administration or topical application of phenylephrine to the mucosa, constriction of blood vessels in the nasal mucosa relieves nasal congestion associated with allergy or head colds. Following oral administration, nasal decongestion may occur within 15 or 20 minutes and may persist for up to 4 hours.

Distribution and metabolism

It is subject to extensive presystemic metabolism in the gut wall and therefore has a systemic bioavailability of approximately 40% relative to intravenous dosing. Following oral administration, peak plasma concentrations are achieved in 1 - 2 hours. The mean plasma half-life is in the range 2 - 3 hours.
The volume of distribution is large (200 to litres). Penetration of the brain and excretion in breast milk appear to be minimal. Phenylephrine does not cross the placenta. The extent of protein binding is unknown. Phenylephrine is extensively metabolised in the gut wall and liver. The principal routes of metabolism are sulphation and glucuronidation of the 3-hydroxyl group and oxidative deamination by monoamine oxidase to 3-hydroxymandelic acid and 3-hydroxyphenylglycol. Sulphate conjugates are formed from the metabolites.

Elimination

Excretion is via the kidneys.

Pharmacokinetics of Paracetamol:

Paracetamol is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 10 to 60 minutes after oral administration.

Paracetamol is distributed into most body tissues. Plasma protein binding is negligible at usual therapeutic doses but increases with increasing doses. The elimination half-life varies from about 1 to 3 hours.

Paracetamol is metabolised extensively in the liver and excreted in the urine mainly as inactive glucuronide and sulfate conjugates. Less than 5% is excreted unchanged. The metabolites of paracetamol include a minor hydroxylated intermediate which has hepatotoxic activity. This intermediate metabolite is detoxified by conjugation with glutathione; however, it can accumulate following paracetamol overdosage (more than 150mg/kg or 10g total paracetamol ingested) and if left untreated can cause irreversible liver damage.

Paracetamol is metabolised differently by premature infants, newborns, infants and young children compared to adults, the sulfate conjugate being predominant.

5.3 Preclinical Safety Data

Toxicity & Carcinogenicity:

Animal or Human toxicological studies of Contus Plus Paediatric Suspension to assess the carcinogenic and mutagenic potential, or the effect on fertility have not been performed. But individual active ingredients of the combination have been tested and the reports have been published for various parameters.

CHLORPHENAMINE MALEATE:

Toxicology and carcinogenesis studies of chlorpheniramine maleate (99% pure), a widely used antihistaminic drug in human and veterinary medicine, were conducted by administering this chemical in deionized water by gavage to groups of 50 male and 50 female F344/N rats and B6C3F1 mice, 5 days per week for 103 weeks.
The doses used were: male rats-- 0, 15, or 30 mg/kg; female rats-- 0, 30, or 60 mg/kg; male mice-- 0, 25, or 50 mg/kg; female mice-- 0, 100, or 200 mg/kg. The selection of these doses was based largely on data from 14-day or 16-day studies and 13-week studies in which reduced body weight gain and reduced survival occurred at higher doses.
Doses used in the 2-week studies ranged from 40 to 640 mg/kg in rats and 25 to 800 mg/kg in mice; in the 13-week studies, doses ranged from 3.75 to 60 mg/kg in rats and
12.5 to 200 mg/kg in mice. The recommended human adult daily oral dose of chlorpheniramine maleate is up to 0.32 mg/kg.

Mutagenicity:

Chlorpheniramine maleate was not mutagenic to Salmonella strains TA98, TA100, TA1535, or T1537 in the presence or absence of S9 metabolic activation systems prepared from the liver of Aroclor 1254-treated male Sprague-Dawley rats or male Syrian hamsters. Chlorpheniramine maleate did not induce forward mutations at the TK locus of L5178Y mouse lymphoma cells with or without metabolic activation. In Chinese hamster ovary cells in culture, chlorpheniramine maleate induced a weak but reproducible increase in sister-chromatid exchanges in the absence of exogenous metabolic activation.
Chromosomal aberrations were induced at the highest dose tested but only in the presence of S9 from Aroclor 1254-induced Sprague-Dawley male rat liver. An audit of the experimental data was conducted for these 2-year carcinogenesis studies on chlorpheniramine maleate. No data discrepancies were found that influenced the final interpretations.
Under the conditions of these 2-year gavage studies, there was no evidence of carcinogenicity for F344/N rats or B6C3F1 mice of either sex administered chlorpheniramine maleate in deionized water, 5 days per week for 2 years. Due to high mortality in high dose female rats and high dose male mice, the sensitivity of these groups to detect a carcinogenic response was reduced.

Chlorpheniramine maleate had a proliferative effect in the thyroid gland of female mice, as shown by the increased incidences of follicular cell cysts and hyperplasia in both low dose and high dose groups.

Teratogenicity:

In a study in rats with chlorpheniramine maleate, a reduction in fertility was observed in female rats at doses approximately 67 times the human dose. More recent studies in rabbits and rats, using more appropriate methodology and doses up to approximately 50 and 85 times the human dose, showed no reduction in fertility.

PHENYLEPHRINE HYDROCHLORIDE:

Toxicology and carcinogenesis studies of Phenylephrine hydrochloride were conducted by administering diets containing the chemical (99% pure) to F344/N rats and B6C3F1 mice of each sex in studies of 14 days, 12 weeks, and 2 years. In the 14-day studies, no toxic effects were seen in rats or mice fed diets containing up to 2,000 ppm Phenylephrine hydrochloride.

Mutagenicity:

Phenylephrine hydrochloride was not mutagenic in four strains of Salmonella typhimurium (TA100, TA1535, TA1537, and TA98) with or without Aroclor 1254-induced liver S9 from male Sprague-Dawley rats or male Syrian hamsters. The results of mutagenicity studies of Phenylephrine hydrochloride were equivocal in the mouse lymphoma L5178Y/TK$^{+/-}$ assay

in the absence of S9; it was not tested in the presence of S9. Phenylephrine hydrochloride induced sister-chromatid exchanges (SCEs) but not chromosomal aberrations in Chinese hamster ovary cells. The increase in SCEs was seen only in the absence of metabolic activation with S9.
An audit of the experimental data was conducted for the 2-year studies of phenylephrine hydrochloride. No data discrepancies were found that influenced the final interpretations.
Under the conditions of these 2-year studies, there was no evidence of carcinogenicity of phenylephrine hydrochloride for male B6C3F1 mice given 1,250 or 2,500 ppm in feed. Survival of high dose male rats was greater than that of controls, and the incidences of mononuclear cell leukemia and pheochromocytomas were lower in dosed than in control male rats. Inflammation was observed more frequently in the liver and prostate gland of dosed male rats than in controls.

Teratogenicity:

A study in rabbits indicated that continued moderate overexposure to phenylephrine (3 mg/day) during the second half of the pregnancy (22nd day of gestation to delivery) may contribute to perinatal wastage, prematurity, premature labor, and possibly fetal anomalies; when phenylephrine (3 mg/day) was given to rabbits during the first half of the pregnancy (3rd day after mating for seven days), a significant number gave birth to litters of low birth weight. Another study showed that phenylephrine was associated with anomalies of aortic arch and with ventricular septal defect in the chick embryo.

PARACETAMOL:

Human carcinogenicity data

None of six studies from Australia, Europe and North America, including a very large international study, found a consistent association between renal-cell cancer and regular intake of paracetamol at any level.

Animal carcinogenicity data

Paracetamol was tested for carcinogenicity by oral administration in mice and rats. An early study indicated an increased incidence of liver adenomas and carcinomas at a markedly toxic dose in mice of one strain; however, this result was not corroborated in a later study in mice, also at a dose greater than the maximal tolerated dose. A more recent, well-conducted study showed no evidence of a carcinogenic effect in mice. Paracetamol had no carcinogenic effect in rats of several strains, but in rats of one inbred strain, increased incidences of liver and bladder neoplasms were recorded in males at the high dose and an increased incidence of bladder tumours in females at the low dose. A more recent, well-conducted study showed no treatment-related carcinogenic effect in rats. Paracetamol did not promote urinary bladder carcinogenesis in rats and reduced the incidence of intestinal tumours in a two-stage model of intestinal carcinogenesis in rats. It enhanced the incidence of renal adenomas induced by one renal carcinogen but not those induced by another.

Other relevant data

In humans, an association was reported in two case–control studies between daily use of paracetamol and renal disease; however, a causal relationship has not been established. Humans and rodents exposed to doses of paracetamol well above the therapeutic range have experienced centrilobular hepatotoxicity and nephrotoxicity involving the proximal renal tubule.

Teratogenicity:

Paracetamol does not present a teratogenic risk to humans at doses associated with severe maternal toxicity. It did not affect reproductive performance of mice in a continuous breeding protocol, although growth and birth weights were reduced. Sperm abnormalities have been observed in mice. Although paracetamol does cross the placenta the occasional use of therapeutic doses in healthy women does not seem to be associated with an increased risk of malformation and has not been proved to be teratogenic. There seems to be the same degree of renal and hepatotoxicity in the baby as in the mother, so large doses of paracetamol that cause severe maternal toxicity have been associated with foetal kidney and liver damage.

There is structural damage (i.e. affecting organ formation) in a 1st trimester exposure and functional damage (i.e. Affecting organ maturation and/or function) in 2nd and 3rd trimester exposures. There is also an association with foetal anaemia and neonatal jaundice if the overdose is taken near term.

Mutagenicity &Genotoxicity:

The results of studies of the cytogenetic effects of paracetamol in humans are inconclusive. Paracetamol induced sister chromatid exchange in human cells *in vivo*, and it was aneugenic and induced chromosomal aberrations but not micronuclei in mammalian cells *in vivo*. It induced DNA single-strand breaks in mice treated *in vivo*. Paracetamol induced sister chromatid exchange and chromosomal aberrations in human cells *in vitro*. It weakly induced cell transformation in a mouse cell line. It induced chromosomal aberrations, micronuclei and sister chromatid exchange in mammalian cells *in vitro*. It did not induce gene mutation, and the results of tests in mammalian cells *in vitro* for unscheduled DNA synthesis and DNA damage were inconclusive. Overall, paracetamol was genotoxic in mammalian cells *in vivo* and *in vitro*. It was not mutagenic to insects but was clastogenic in plant cells. It was not mutagenic in any standard assay in bacteria.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Pregelatinised Starch, Microcrystalline Cellulose, Maize Starch, Gelatin, Sodium Methyl Hydroxybenzoate, Sunset Yellow Supra, Purified Talc, Magnesium Stearate & Purified Water.

6.2 Incompatibilities

None.

6.3 Shelf Life

36 months

6.4 Special Precaution for Storage

Do not store above 30°C. Protect from light. Keep out of reach of children.

6.5 Nature and Contents of Container

1 x 10's blister strip is packed in a carton with pack insert. 10 x 10's blister strip is packed in a carton with pack insert.
1 x 6's blister strip is packed in a catch cover; 50 such catch covers packed in an outer carton with pack insert.

6.6 Special Precautions for Disposal

None.

7. Marketing authorisation holder:

Manufactured & Marketed by:

Stedman Pharmaceuticals Pvt Ltd

C-4, Sidco Pharmaceutical Complex, Alathur,

Thiruporur, Kancheepuram District,

603110, Tamil Nadu,

India

8. Marketing authorisation number:

H2010/22090/421/R1

9. DATE OF PREQUALIFICATION/RENEWAL OF PREQUALIFICATION:

13/July/2026

10. DATE OF REVISION OF THE TEXT:

January 2025