Summary of Product Characteristics
(Product Data Sheet)

APFLU SYRUP (Chlorphenamine Maleate, Paracetamol and Vitamin C Syrup)

1. Name of the Finished Pharmaceutical Product

1.1 **Product Name: APFLU SYRUP (**Chlorphenamine Maleate, Paracetamol and Vitamin C Syrup)

1.2 Strength : Chlorphenamine Maleate BP 0.50 mg
Paracetamol BP 120 mg
Vitamin C BP 50 mg
Flavoured syrup base q.s.
Colour: Caramel

1.3 Pharmaceutical Dosage Form : Syrup

2. Qualitative & Quantitative Composition:

Ingredients	Theoretical quantity per 5 mL in mg
Paracetamol	120.00
Ascorbic acid*	82.50
Chlorphenamine Maleate**	0.52
Sugar Commercial	2750.00
Glycerol	250.00
Propylene Glycol	1000.00
Methyl Hydroxybenzoate	9.00
Propyl Hydroxybenzoate	1.00
Sodium Metabisulfite	12.50
Sodium Chloride	25.00
Saccharin Sodium	15.00
Mango Flavour ASV	25.00
Liquid Caramel Colour	15.00
Disodium Edetate	1.00
Sodium Dihydrogen Phosphate Dihydrate	2.50
Disodium Hydrogen Phosphate Dihydrate	78.00
Hyflosupercel***	-
Purified Water#	-

* 65.0% overages included.
** 5.0% overages included
*** Not included in the formulation. To be used for filtration purpose only.
# Purified Water confirms to the specification of BP/USP/Ph.Eur/IH

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BP : British Pharmacopoeia
USP : United States Pharmacopoeia
IH : In-house Specification
Ph.Eur : European Pharmacopoeia

3. Pharmaceutical Form:

Brown to light brown coloured syrup with characteristic odour and taste.

4. Clinical Particulars

4.1 Therapeutic Indications:

Apflu Syrup (Acetaminophen, chlorpheniramine, and Vit. C) is a combination medicine used to treat headache, fever, body aches, runny or stuffy nose, sneezing, itching, watery eyes, and sinus congestion caused by allergies, the common cold, or the flu.

Also indicated for the reduction of toothache.

4.2 Posology and Method of Administration:

Oral administration only
Do not exceed the stated dose or frequency of dosing

Children

- 01 – 02 Years: 5 ml x 4 times daily
- 02 – 08 Years: 10 ml x 4 times daily
- 08 – 10 Years: 15 ml x 4 times daily
- 10 – 12 Years: 20 ml x 4 times daily

4.3 Contraindications:

- Hypersensitivity to antihistamines or paracetamol or to any of the excipients
- Patients with severe hepatic dysfunction.
- The anticholinergic properties of chlorphenamine are intensified by monoamine oxidase inhibitors (MAOIs). Therefore, contra-indicated in patients who have been treated with MAOIs within the last fourteen days.
- Ascorbic acid should not be given to patients with hyperoxaluria.

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4.4 Special Warning and Precautions for Use:

Chlorphenamine

Chlorphenamine, in common with other drugs having anticholinergic effects, should be used with caution in epilepsy; raised intra-ocular pressure including glaucoma; prostatic hypertrophy; severe hypertension or cardiovascular disease; bronchitis, bronchiectasis and asthma; hepatic impairment; renal impairment. Children and the elderly are more likely to experience the neurological anticholinergic effects and paradoxical excitation (e.g. increased energy, restlessness, nervousness). Avoid use in elderly patients with confusion.
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.
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

Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.
Do not give with any other paracetamol-containing products.
Medical monitoring is required in patients with impaired renal or hepatic functions because various adverse events attributed to propylene glycol have been reported such as renal dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction.

Ascorbic Acid

Increased intake of ascorbic acid over a prolonged period may result in an increased renal clearance of ascorbic acid, and deficiency may result if the intake is reduced or withdrawn rapidly.

Interference with serological testing

Ascorbic acid may interfere with tests and assays for urinary glucose, giving false-negative results with methods utilising glucose oxidase with indicator (e.g. Labstix, Tes-Tape) and false-positive results with neocuproine methods.

Estimation of uric acid by phosphotungstate or uricase with copper reduction and measurement of creatinine in non-deproteinised serum may also be affected.

High doses of ascorbic acid may give false-negative reading in faecal occult blood tests.

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4.5 Interactions with other medicinal products and other forms of Interactions :

Concurrent use of chlorphenamine and hypnotics or anxiolytics may cause an increase in sedative effects; concurrent use of alcohol may have a similar effect therefore medical advice should be sought before taking chlorphenamine concurrently with these medicines.
Chlorphenamine inhibits phenytoin metabolism and can lead to phenytoin toxicity.
The anticholinergic effects of chlorphenamine are intensified by MAOIs
The hepatotoxicity of Paracetamol, particularly after overdosage, may be increased by drugs, which induce liver microsomal enzymes such as barbiturates, tricyclic antidepressants, and alcohol.
Chronic alcohol intake can increase the hepatotoxicity of paracetamol overdose and may have contributed to the acute pancreatitis reported in one patient who had taken an overdose of paracetamol. Acute alcohol intake may diminish an individual's ability to metabolize large doses of paracetamol, the plasma half-life of which can be prolonged.
The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by colestyramine.
The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.
Antivirals: Regular use of Paracetamol possibly reduces metabolism of Zidovudine (increased risk of neutropenia).
The use of drugs that induce hepatic microsomal enzymes such as anticonvulsants and oral contraceptives may increase the extent of metabolism of paracetamol resulting in reduced plasma concentrations of the drug and a faster elimination rate.

Ascorbic acid increases the renal excretion of amphetamine. The plasma concentration of ascorbate is decreased by smoking and oral contraceptives.
Ascorbic acid increases the absorption of iron.
Concomitant administration of aspirin and ascorbic acid may interfere with absorption of ascorbic acid. Renal excretion of salicylate is not affected and does not lead to reduced anti-inflammatory effects of aspirin.
Concomitant administration of aluminium-containing antacids may increase urinary aluminium elimination. Concurrent administration of antacids and ascorbic acid is not recommended, especially in patients with renal insufficiency.
Co-administration with amygdalin (a complementary medicine) can cause cyanide toxicity.
Concurrent administration of ascorbic acid with desferrioxamine enhances urinary iron excretion. Cases of cardiomyopathy and congestive heart failure have been reported in patients with idiopathic haemochromatosis and thalassaemias receiving desferrioxamine who were subsequently given ascorbic acid. Ascorbic acid should be used with caution in these patients and cardiac function monitored.
Ascorbic acid may interfere with biochemical determinations of creatinine, uric acid and glucose in samples of blood and urine.

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4.6 Pregnancy and Lactation:

Pregnancy

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

Lactation

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

4.7 Effects on Ability to Drive and Use Machine:

The anticholinergic properties of chlorphenamine in Apflu Syrup may cause drowsiness, dizziness, blurred vision and psychomotor impairment, which can seriously hamper the patients' ability to drive and use machinery.

Ascorbic acid has no known effect on an individual's ability to drive or operate machinery.

4.8 Undesirable Effects:

Chlorphenamine

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:

System Organ Class	Adverse Reaction	Frequency
Nervous system disorders*	Sedation, somnolence	Very common
	Disturbance in attention, abnormal coordination, dizziness headache	Common
Eye disorders	Blurred Vision	Common
Gastrointestinal disorders	Nausea, dry mouth	Common
	Vomiting, abdominal pain, diarrhoea, dyspepsia	Unknown
Immune system disorders:	Allergic reaction, angioedema, anaphylactic reactions	Unknown
Metabolism and nutritional disorders	Anorexia	Unknown

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Blood and lymphatic system disorders	Haemolytic anaemia, blood dyscrasias	Unknown
Musculoskeletal and connective tissue disorders	Muscle twitching, muscle weakness	Unknown
Psychiatric disorders	Confusion*, excitation*, irritability*, nightmares*, depression	Unknown
Renal and urinary disorders	Urinary retention	Unknown
Skin and subcutaneous disorders	Exfoliative dermatitis, rash, urticaria, photosensitivity	Unknown
Respiratory, thoracic and mediastinal disorders	Thickening of bronchial secretions	Unknown
Vascular disorders	Hypotension	Unknown
Hepatobiliary disorders	Hepatitis, including jaundice	Unknown
Ear and labyrinth disorders	Tinnitus	Unknown
Cardiac disorders	Palpitations, tachycardia, arrhythmias	Unknown
General disorders and administration site conditions	Fatigue	Common
	Chest tightness	Unknown

*Children and the elderly are more susceptible to neurological anticholinergic effects and paradoxical excitation (eg increased energy, restlessness, nervousness)

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 causality related to paracetamol.

Very rare cases of serious skin reactions have been reported.

Cases of acute pancreatitis have been reported. Paracetamol has been widely used and reports of adverse reactions are rare, and are generally associated with overdosage.

Allergic reactions occur occasionally.

Chronic hepatic necrosis has been reported in a patient who took daily therapeutic doses of paracetamol for about a year and liver damage has been reported after daily ingestion of excessive amounts for shorter periods. A review of a group of patients with chronic active hepatitis failed to reveal differences in the abnormalities of liver function in those who were long-term users of paracetamol nor was the control of the disease improved after paracetamol withdrawal.

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Low-level transaminase elevations may occur in some patients taking therapeutic doses of paracetamol; these are not accompanied with liver failure and usually resolve with continued therapy or discontinuation of paracetamol.
Nephrotoxic effects are uncommon and have not been reported in association with therapeutic doses, except after prolonged administration.

Ascorbic acid
Nervous system disorders: headache.
Vascular disorders: flushing.
Gastrointestinal disorders: nausea, vomiting and stomach cramps. Large doses of ascorbic acid may cause diarrhoea.
Skin and subcutaneous tissue disorders: redness of skin.
Renal and urinary disorders: Patients known to be at risk of hyperoxaluria should not ingest ascorbic acid doses exceeding 1g daily as there may be increased urinary oxalate excretion. However, such risk has not been demonstrated in normal, non-hyper oxaluric individuals. Ascorbic acid has been implicated in precipitating haemolytic anaemia in certain individuals deficient of glucose-6-phosphate dehydrogenase.
Increased intake of ascorbic acid over a prolonged period may result in increased renal clearance of ascorbic acid, and deficiency may result if the intake is reduced or withdrawn rapidly. Doses of more than 600mg daily have a diuretic effect.

4.9 Overdose:
Chlorphenamine

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 centres 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.

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Paracetamol

Liver damage is possible in adults who have taken 10g or more of paracetamol. Ingestion of 5g or more of paracetamol may lead to liver damage if the patient has risk factors (see below).
Risk factors
If the patient
a) Is on long term treatment with carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.
Or
b) Regularly consumes ethanol in excess of recommended amounts
Or
c) Is likely to be glutathione depleted e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms

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 encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Management

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines, see BNF overdose section.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion, (earlier concentrations are unreliable). Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol; however, the maximum protective effect is obtained up to 8 hours post-ingestion. The effectiveness of the antidote declines sharply after this time. If required, the patient should be given intravenous N-acetylcysteine in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for

remote areas, outside hospital. Management of patients who present with serious hepatic dysfunction beyond 24h from ingestion should be discussed with the NPIS or a liver unit.

Ascorbic acid

Symptoms

At doses of over 3g per day unabsorbed ascorbic acid is mainly excreted unmetabolised in the faeces. Absorbed ascorbic acid additional to the body's needs is rapidly eliminated. Large doses of ascorbic acid may cause diarrhoea and the formation of renal oxalate calculi. Symptomatic treatment may be required.

Ascorbic acid may cause acidosis or haemolytic anaemia in certain individuals with a deficiency of glucose 6-phosphate dehydrogenase. Renal failure can occur with massive ascorbic acid overdosage.

Management

Gastric lavage may be given if ingestion is recent otherwise general supportive measure should be employed as required.

5. Pharmacological properties

5.1 Pharmacodynamic Properties:

Chlorphenamine

Mechanism of Action

Chlorphenamine is a potent antihistamine (H1-antagonist).
Antihistamines diminish or abolish the actions of histamine in the body by competitive reversible blockade of histamine H1-receptor sites on tissues. Chlorphenamine also has anticholinergic activity.
Antihistamines act to prevent the release of histamine, prostaglandins and leukotrines and have been shown to prevent the migration of inflammatory mediators. The actions of chlorphenmine include inhibition of histamine on smooth muscle, capillary permeability and hence reduction of oedema and wheal in hypersensitivity reactions such as allergy and anaphylaxis.

Paracetamol

Mechanism of Action

The mechanism of analgesic action has not been fully determined. Paracetamol may act predominantly by inhibiting prostaglandin synthesis in the central nervous system (CNS) and, to a lesser extent, through a peripheral action by blocking pain impulse generation. The peripheral action may also be due to inhibition of prostaglandin synthesis or to inhibition of the synthesis or actions of other substances that sensitise pain receptors to mechanical or chemical stimulation.

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Paracetamol probably produces antipyresis by acting centrally 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.

Ascorbic acid
Mechanism of Action
Ascorbic acid is a source of vitamin C, which may be beneficial during infection when vitamin C levels are believed to fall.

5.2 Pharmacokinetic Properties:

Chlorphenamine:
Absorption
Chlorphenamine is well absorbed from the gastro-intestinal tract, following oral administration. The effects develop within 30 minutes, are maximal within I to 2 hours and last 4 to 6 hours. The plasma half-life has been estimated to be 12 to 15 hours.
Chlorphenamine is metabolised to the monodesmethyl and didesmethyl derivatives. About 22% of an oral dose is excreted unchanged in the urine.

Metabolism
Chlorphenamine is metabolised to the monodesmethyl and didesmethyl derivatives

Excretion
About 22% of an oral dose is excreted unchanged in the urine.

Paracetamol:

Oral absorption is rapid and almost complete; it may be decreased if Paracetamol is taken following a high carbohydrate meal.
There is no significant protein binding with doses producing plasma concentrations of below 60mcg (µg)/ml, but may reach moderate levels with high or toxic doses.
Approximately 90 - 95% of a dose is metabolised in the liver, primarily by conjugation with glucuronic acid, sulphuric acid and cysteine. An intermediate metabolite, which may accumulate in overdosage after primary metabolic pathways become saturated, is hepatotoxic and possibly nephrotoxic.
Half-life is 1 to 4 hours; does not change with renal failure but may be prolonged in acute overdosage, in some forms of hepatic disease, in the elderly, and in the neonate; may be somewhat shortened in children.
Time to peak concentration, 0.5 - 2 hours; peak plasma concentrations, 5 - 20mcg (µg)/ml (with doses up to 650mg); time to peak effect, 1- 3 hours; duration of action, 3- 4 hours.
Elimination is by the renal route, as metabolites, primarily conjugates, 3% of a dose may be excreted unchanged.

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Peak concentration of 10 - 15mcg(µg)/ml have been measured in breast milk, 1 - 2 hours following maternal ingestion of a single 650mg dose. Half-life in breast milk is 1.35 - 3.5 hours.

Ascorbic acid
Ascorbic acid is readily absorbed from the gastrointestinal tract and widely distributed in the body tissues. Ascorbic acid is reversibly oxidised to dehydro ascorbic acid; some is metabolised to ascorbate-2-sulphate, which is inactive, and oxalic acid, which are excreted in the urine. Ascorbic acid crosses the placenta and is distributed into breast milk.

5.3 Preclinical Study:
Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

6. Pharmaceutical particulars

6.1 List of Excipients:
Sugar Commercial IH, Glycerol BP, Propylene Glycol BP, Methyl Hydroxybenzoate BP, Propyl Hydroxybenzoate BP, Sodium Metabisulfite BP, Sodium Chloride BP, Saccharin Sodium BP Mango Flavour ASV IH, Liquid Caramel Colour IH, Disodium EDTA, Sodium Dihydrogen Phosphate Dehydrate BP, Disodium Hydrogen Phosphate Dihydrate BP, Hyflosupercel IH and Purified Water.

6.2 Incompatibilities: Not applicable

6.3 Shelf life: 24 months

6.4 Special Precautions for Storage: Not-available.

6.5 Storage Condition: Keep in cool place at temperature below 30°C. Protect from light.

6.6 Nature and Contents of Container:
Available in 100 ml Amber Glass bottle in a carton along with pack insert.

7. Marketing Authorization Holder:

Ajanta Pharma Limited
Ajanta House,
Charkop, Kandivli (West),
Mumbai- 400 067,
India

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Marketing Authorization Numbers: PMPB/PL303/41

8. **Date of First Authorization/ Renewal of the Authorization:** Nov 05, 2018.

9. **Date of Revision of Text:** Apr 2022.