Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Uniflu Plus with Vitamin C Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Uniflu Plus tablet contains:

Caffeine 30.0 mg
Codeine phosphate hemihydrate 10.0 mg
Diphenhydramine hydrochloride 15.0 mg
Paracetamol 500.0 mg
Phenylephrine hydrochloride 10.0 mg

For a full list of excipients, see section 6.1

Each Vitamin C tablet contains:

Ascorbic acid 300.0 mg
(as ascorbic acid/sodium ascorbate)

Excipients: contains 5.00mg lactose and 270.0mg sucrose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Uniflu Plus:
Film-coated tablet.
White, oblong, film-coated tablet.

Vitamin 'C':
Chewable tablet.
Yellow, biconvex, circular, plain, lemon flavoured chewable tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Uniflu Plus:

For the symptomatic relief from the discomforts associated with influenza and colds i.e. nasal and sinus congestion, headache, fever, aching limbs, coughing and runny nose.

Vitamin 'C':

For use as a vitamin C supplement during cold and influenza infections.

4.2 Posology and method of administration

Uniflu Plus:

Adults: One Uniflu Plus tablet to be swallowed whole with water, followed by one tablet every six hours.

Not more than four tablets of Uniflu Plus to be taken in 24 hours.

Elderly: As adult dose.

Children: Under 12 years – Not recommended.

Over 12 years – One tablet every eight hours.

Not more than three tablets of Uniflu Plus to be taken in 24 hours.

Vitamin 'C'

Adults: One Vitamin 'C' tablet to be swallowed whole, sucked or chewed every six hours.

Elderly: As Adult dose.

Children: Over 12 years – One tablet to be swallowed whole, sucked or chewed every eight hours.

Under 12 years – Not recommended.

Codeine should be used at the lowest effective dose for the shortest period of time.

The duration of treatment should be limited to 3 days and if no effective relief is achieved the patients/carers should be advised to seek the views of a physician.

Paediatric population:

Children aged 12 years to 18 years:
The recommended codeine dose with this product for children 12 years and older, should be 10mg every 8 hours to a maximum dose of codeine of 30 mg daily. Codeine is not recommended for use in children aged 12 years to 18 years with compromised respiratory function for the symptomatic treatment of influenza and colds (see section 4.4).

Children aged less than 12 years:
Codeine is contraindicated in children below the age of 12 years for the symptomatic treatment of influenza and colds (see section 4.3).

4.3 Contraindications

Uniflu Plus:
Hypersensitivity to paracetamol or any of the other constituents. The phenylephrine content of Uniflu Plus tablets contraindicates their use in hyperthyroidism and hypertension, cardiovascular and coronary disease and should not be given to patients being treated with monoamine oxidase inhibitors or within fourteen days of stopping such treatment. Phenylephrine also contraindicates use in patients with glaucoma or urinary retention and use in patients who are currently receiving other sympathomimetic drugs.

Uniflu Plus tablets are contraindicated in chronic obstructive airways disease.

Vitamin C:
Hypersensitivity to ascorbic acid or any of the other constituents

Codeine:

- In all paediatric patients (0-18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome due to an increased risk of developing serious and life-threatening adverse reactions (see section 4.4).
- In children below the age of 12 years for the symptomatic treatment of influenza and colds due to an increased risk of developing serious and life-threatening adverse reactions.
- In women during breastfeeding (see section 4.6).
- In patients for whom it is known they are CYP2D6 ultra-rapid metabolisers.

4.4 Special warnings and precautions for use

Uniflu Plus:

Regarding paracetamol, Uniflu Plus should be administered with care to patients with severe renal or severe hepatic impairment. The hazard of overdose is greater in those with non-cirrhotic alcoholic liver disease. Caution is required in patients with epilepsy and prostatic hypertrophy.

CYP2D6 metabolism
Codeine is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect will not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an extensive or ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at commonly prescribed doses. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels.

General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life-threatening and very rarely fatal.
Estimates of prevalence of ultra-rapid metabolisers in different populations are summarized below:

Population	Prevalence %
African/Ethiopian	29%
African American	3.4% to 6.5%
Asian	1.2% to 2%
Caucasian	3.6% to 6.5%
Greek	6.0%
Hungarian	1.9%
Northern European	1%-2%

Post-operative use in children
There have been reports in the published literature that codeine given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life-threatening adverse events including death (see also section 4.3). All children received doses of codeine that were within the appropriate dose range; however there was evidence that these children were either ultra-rapid or extensive metabolisers in their ability to metabolise codeine to morphine.

Children with compromised respiratory function
Codeine is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of morphine toxicity.

Regarding codeine, prolonged regular use, except under medical supervision, may lead to physical and psychological dependence (addiction) and result in withdrawal symptoms, such as restlessness and irritability once the drug is stopped. Do not exceed the stated dose. Keep out of the reach of children.

If symptoms persist or worsen consult your doctor. Patients receiving other regular medication especially medication for depression should be warned to consult their physician before using this product. Patients should be advised not to take other paracetamol-containing products concurrently.

The product should not be taken for persistent or chronic cough such as occurs with smoking, asthma or emphysema or if cough is accompanied by excessive mucous/phlegm unless directed by the doctor.

The physician or pharmacist should check that sympathomimetic containing preparations are not simultaneously administered by several routes i.e. orally and topically (nasal, aural and eye preparations).

Sympathomimetic-containing products should be used with great care in patients suffering from angina and in patients receiving phenothiazines or tricyclic antidepressants.

Sympathomimetic-containing products should be used with caution in patients receiving digitalis, beta-adrenergic blockers, guanethidine, reserpine, methyldopa or anti-hypertensive agents.

Concurrent use with halogenated anaesthetic agents such as chloroform, cyclopropane, halothane, enflurane or isoflurane may provoke or worsen ventricular arrhythmias.

Sympathomimetic-containing products may act as cerebral stimulants giving rise to insomnia, nervousness, hyperpyrexia, tremor and epileptiform convulsions.

Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patients with severe illness such as severe renal impairment and sepsis, or in patients with malnutrition or other sources of glutathione deficiency (e.g. chronic alcoholism) who were treated with paracetamol at therapeutic dose for a prolonged period or a combination of paracetamol and flucloxacillin. If HAGMA due to pyroglutamic acidosis is suspected, prompt discontinuation of paracetamol and close monitoring, including measurement of urinary 5-oxoproline, is recommended. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as underlying cause of HAGMA in patients with multiple risk factors.

Vitamin C:

As this medicine contains lactose and sucrose, patients with rare hereditary problems of fructose or galactose intolerance, glucose-galactose malabsorption, the Lapp lactase deficiency or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Refer to these interactions in Section 4.4.

Uniflu Plus:

Alcohol and other central nervous system depressants can potentiate the sedative effect of Uniflu Plus tablets. Patients are warned to avoid alcoholic drink whilst using the product. Phenylephrine may antagonise the effects of concurrent antihypertensive therapy. The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine.

Paracetamol may cause a marginal increase in blood levels of chloramphenicol.

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

The effects of anticlinergics e.g. some psycotropic drugs and atropine, may be potentiated giving rise to tachycardia, mouth dryness, gastrointestinal disturbances e.g. colic, urinary retention and headache.

Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis due to pyroglutamic acidosis, especially in patients with risks factors (see section 4.4).

Vitamin C:

There are no known clinically significant interactions with other medicaments.

4.6 Fertility, pregnancy and lactation

Pregnancy

Uniflu Plus:

The safe use of Uniflu Plus tablets in pregnancy has not been established. They should not, therefore, be used in pregnancy except under close medical supervision.
A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity from paracetamol. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. Patients should follow the advice of their doctor regarding its use.

Vitamin C:

Vitamin C may be administered to pregnant women under the supervision of a doctor.

Breast-feeding

Uniflu Plus:

Uniflu Plus tablets should be avoided in nursing mothers.

Paracetamol is excreted in breast milk but not in a clinically significant amount.

Codeine is contraindicated in women during breastfeeding (see section 4.3).
At normal therapeutic doses codeine and its active metabolite may be present in breast milk at very low doses and is unlikely to adversely affect the breast fed infant. However, if the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of the active metabolite, morphine, may be present in breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant, which may be fatal.

If symptoms of opioid toxicity develop in either the mother or the infant, then all codeine containing medicines should be stopped and alternative non-opioid analgesics prescribed. In severe cases consideration should be given to prescribing naloxone to reverse these effects.

Vitamin C:

Vitamin C may be administered to lactating women under the supervision of a doctor.

Fertility
No data available.

4.7 Effects on ability to drive and use machines

Uniflu Plus:

Drowsiness may be experienced during treatment with Uniflu Plus tablets and patients are advised not to drive or operate machinery if affected.

Vitamin C:

Vitamin C has no or negligible influence on the ability to drive or use machines.

4.8 Undesirable effects

Uniflu Plus:

Side effects are listed below by body system in order of decreasing severity.

Vascular Disorders
Hypertension

Gastrointestinal Disorders
Gastro-intestinal disturbances, dry mouth.

Nervous System Disorders
Headache, tremors

Blood and Lymphatic Disorders
Blood disorder, Thrombocytopenia, Agranulocytosis

Psychiatric Disorders
Insomnia and nervousness

Eye Disorders
Vision blurred.

Renal and Urinary Disorders
Urinary retention.

Immune System Disorders/Skin and Subcutaneous Tissue Disorders
Hypersensitivity e.g., skin rash. Very rare cases of serious skin reactions have been reported.

Metabolism and nutrition disorders
High anion gap metabolic acidosis, frequency – not known.

Description of selected adverse reactions

High anion gap metabolic acidosis

Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol (see section 4.4). Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients.

Please refer to Section 4.5 for details on interaction with other medicinal products and other forms of interaction.

Vitamin C:

No undesirable effects have been reported.

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 via HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Uniflu Plus:

Overdosage may lead to tachycardia, hypertension, nausea, vomiting, delayed onset hepatic failure due to paracetamol and respiratory depression due to codeine.

Immediate medical advice should be sought in the event of an overdose, even if you feel well, because of the risk of delayed, serious liver damage.

Treatment consists of supportive measures, gastric lavage, as well as correction of any fluid or electrolyte imbalance. Intravenous N-acetylcysteine and naxolone may be needed as antidotes in severe cases. In cases of severe hypertension, intravenous phentolamine may be required.

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, 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 in excess of recommended doses 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.

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 and any patient who has ingested a significant amount of paracetamol in the preceding 4 hours should undergo gastric lavage. Administration of oral methionine or intravenous N-acetylcysteine which may have a beneficial effect up to at least 48 hours after the overdose, may be required. General supportive measures must be available.

Vitamin 'C':

No cases of overdosage have been reported.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Uniflu Plus:

ATC Classification: N02BE51

Caffeine
Caffeine, like other xanthines, stimulates the central nervous system, increases respiration, affects smooth muscle and exerts a diuretic effect. These effects are all thought to be mediated by the inhibition of phosphodiesterase resulting in a raised cyclic AMP concentration. Of the xanthines, caffeine is the most active in stimulating the central nervous system and is principally used for this purpose and has the least diuretic effect. Its action on the central nervous system is mainly on the higher centres producing a condition of wakefulness and increased mental activity. Caffeine may stimulate the respiratory centre and increase the rate and depth of respiration.

Codeine phosphate
Codeine phosphate has analgesic, antidiarrhoeal and antitussive actions. Codeine is the antitussive agent against which all other antitussives are evaluated. Codeine is a centrally acting weak analgesic. Codeine exerts its effect through μ opioid receptors, although codeine has low affinity for these receptors, and its analgesic effect is due to its conversion to morphine. Codeine, particularly in combination with other analgesics such as paracetamol, has been shown to be effective in acute nociceptive pain.

It acts by depressing the central pathways of the cough reflex in the medulla. The dosage of codeine phosphate employed in Uniflu Plus tablets is that which is necessary to produce antitussive action.

Diphenhydramine hydrochloride
Diphenhydramine hydrochloride is an ethanolamine derivative with the properties and use of antihistamine. It is less potent than promethazine hydrochloride but has a shorter duration of action. It has sedative, anti-emetic, anticholinergic and local anaesthetic properties.

Diphenhydramine hydrochloride is a histamine H1-receptor antagonist. It has action on the contraction of smooth muscle and the dilatation and increased permeability of the capillaries. It also has anticholinergic activity.

Paracetamol
Paracetamol has both antipyretic and analgesic activities but no useful anti inflammatory properties. Its mechanism of analgesic effect is not yet defined. Prostaglandin synthetase from the central nervous system is sensitive to paracetamol, explaining its antipyretic effect. It does not, however, have an anti-inflammatory effect as the peripheral tissue prostaglandin synthetase is not affected.

Phenylephrine hydrochloride
Phenylephrine hydrochloride is a sympathomimetic agent with mainly direct effects on adrenergic receptors. It has predominantly α-adrenergic activity and is used to elicit sympathetic responses (vasoconstriction) where there is congestion and inflammation of the nasal mucosa.

Vitamin C:
Ascorbic acid (vitamin C) cannot be synthesised by man, therefore a dietary source is necessary.

Ascorbic acid (vitamin C) acts as a cofactor in numerous biological processes including the hydroxylation of proline to hydroxyproline. In deficiency, the formation of collagen is therefore impaired.

Ascorbic acid (vitamin C) is important in the hydroxylation of dopamine to noradrenaline and in hydroxylations occurring in steroid synthesis in the adrenals.

Ascorbic acid (vitamin C) is a reducing agent in tyrosine metabolism and by acting as an electron donor in the conversion of folic acid to tetrahydrofolic acid is directly involved in the synthesis of purine to thymine.

Ascorbic acid (vitamin C) is also necessary for the incorporation of iron into ferritin.

Ascorbic acid (vitamin C) increases the phagocytic function of leucocytes; it possesses anti-inflammatory activity and promotes wound healing.

Deficiency can cause scurvy. Features include swollen inflamed gums, petechial haemorrhages and subcutaneous bruising.

The deficiency of collagen leads to development of thin watery ground substances in which blood vessels are insecurely fixed and readily ruptured. The supportive components of bone and cartilage are also deficient causing bones to fracture easily and teeth to become loose.

Anaemia commonly occurs probably due to the role of ascorbic acid (vitamin C) in iron metabolism.

5.2 Pharmacokinetic properties

Uniflu Plus:

Caffeine

Caffeine is absorbed erratically from the gastro-intestinal tract and does not appear to accumulate in any particular tissue. It passes readily into the central nervous system and saliva.

Caffeine is almost completely metabolised and is excreted in the urine as 1-methyluric acid, 1-methylxanthine and other metabolites. Only about 1% remains unchanged.

Codeine phosphate

Codeine phosphate is absorbed from the gastro-intestinal tract with peak plasma codeine concentrations produced in about one hour. Codeine is metabolised by O and N-demethylation in the liver to morphine and norcodeine. About 10% of an oral dose is demethylated to morphine. The plasma half life of codeine in healthy volunteers has been found to be about 3.5 hours. Codeine and its metabolites are excreted almost entirely by the kidneys, mainly as conjugates with glucuronic acid.

Diphenhydramine hydrochloride

Diphenhydramine hydrochloride is absorbed from the gastro-intestinal tract, metabolised by the liver and excreted mainly as metabolites in the urine. Any unchanged diphenhydramine is eliminated more rapidly than its metabolites. It has been reported to be 98% bound to plasma proteins with a normal half-life of 4 to 7 hours.

Paracetamol

Paracetamol is a weak acid which is readily absorbed from the gastro-intestinal tract with peak plasma concentration occurring about 30 minutes to 2 hours after ingestion. Following absorption it is mainly biotransformed by conjugation to the sulphate and glucuronide. Plasma-protein binding is negligible at the usual therapeutic concentrations.

The elimination of paracetamol does not appear to follow saturation kinetics. The half-life of paracetamol ranges from 2-4 hours in healthy adults. In adults, the sulphate and glucuronide account for about 90% of the urinary recovery of paracetamol, each metabolite contributing to half this amount. Less than 5% is excreted as unchanged paracetamol.

In the overdose situation, the defence mechanisms of the liver which lead to non-toxic glucuronide and sulphate formation are overwhelmed. Normally minor metabolic pathways therefore participate actively in the overall biotransformation of the drug and these produce hepatoxic metabolites.

Phenylephrine hydrochloride

The bioavailability of phenylephrine is reduced due to first pass metabolism by monoamine oxidase in the gut and liver.

Vitamin 'C':

Ascorbic acid (vitamin C) is a water soluble vitamin which is readily absorbed from the gastro-intestinal tract and is widely distributed in the body tissues.

Ascorbic acid (vitamin C) is reversibly oxidised to dehydroascorbic acid; some is metabolised to ascorbate-2-sulphate, which is inactive, and oxalic acid which are excreted in the urine. Ascorbic acid (vitamin C) in excess of the body's needs is also rapidly eliminated unchanged in the urine.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

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

Uniflu Plus tablets - Cores:
Acacia
Protein S (Byco C) (hydrolysed gelatin)
Alginic acid (E400)
Magnesium stearate
Stearic acid
Sodium starch glycollate (Type A)

Uniflu Plus tablets -Film-coating:
Opadry II White
- contains: polyvinyl alcohol, titanium dioxide (E171), macrogol, talc

Vitamin 'C'tablets:
Saccharin sodium
Stearic acid
Magnesium stearate
Compressible sugar
Lemon flavour E2954 (includes maltodextrin, acacia, lactose)
Quinoline yellow lake 19248 (E104)
Pectin
Hypromellose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package (to protect from moisture).

6.5 Nature and contents of container

The product is presented in press through blisters containing six Uniflu Plus tablets with six Vitamin 'C' tablets. The blister pack is made from PVC/PVdC with a printed aluminium foil lidding.

The product is available in two pack sizes:

i. 12 tablet box containing 1 blister strip
ii. 24 tablet box containing 2 blister strips

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Phoenix Labs
Suite 12, Bunkilla Plaza
Bracetown Business Park
Clonee
Co. Meath.
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1113/006/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30 October 1998

Date of last renewal: 30 October 2008

10 DATE OF REVISION OF THE TEXT

February 2025