UNICURE PHARMACEUTICAL LTD.

SUMMARY OF PRODUCT CHARACTERISTICS

FOR

CURECEE

VITAMIN C PLUS GLUCOSE

(50mg + 150mg) TABLETS

TABLE OF CONTENT

1. Name of the medicinal product

CURECEE (Vitamin C Plus Glucose) 50mg + 150mg

2. Qualitative and quantitative composition

Each CURECEE tablet contains 50 mg of Vitamin C and 150mg of Glucose

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Orange flavoured and coloured square flat lozenge with inscription UNICURE on one side and blank on the other side

4. Clinical particulars

4.1 Therapeutic indications

It is indicated to treat the symptoms of Ascorbic Acid Deficiency (Scurvy), Urinary Acidification and as a nutritional supplement. Ascorbic Acid may be used alone or with other medications.

4.2 Posology and method of administration

Posology

Use the lowest dose for the shortest duration necessary to relieve symptoms.

Adults:

Two lozenge every 2-3 hours up to a maximum of 12 lozenges in 24 hours.

Children over 6 years old:

As above for adults.

Elderly:

There is no need for dosage reduction in the elderly.

Children under 6 years old:

Not suitable for children under 6 years (see section 4.4).

Method of administration

For oral administration. To be dissolved slowly in the mouth.

4.3 Contraindications

Hypersensitivity to any of the ingredients. Stop using ascorbic acid and call your doctor at once if you have:

joint pain,

weakness or tired feeling,

weight loss,

stomach pain;

chills,

fever,

increased urge to urinate,

painful or difficult urination; or

severe pain in your side or lower back,

blood in your urine.

Common side effects may include:

heartburn, upset stomach; or

nausea, diarrhea, stomach cramps.

This is not a complete list of side effects and others may occur. Call your doctor for medical advice about side effects.

4.4 Special warnings and precautions for use

Not to be given to children under 6 years

If symptoms persist, have not improved, or have worsened after 3 days, consult a doctor or health care professional.

Important information about some of the ingredients of this medicine:

This CURECEE contains only very low levels of gluten (from wheat starch). It is regarded as 'gluten-free' and is very unlikely to cause problems if you have coeliac disease.

One lozenge contains no more than 19.36 micrograms of gluten.

If you have wheat allergy (different from coeliac disease) you should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

CURECEE contains fragrance with Citral, Citronellol, d-Limonene, Geraniol and Linalool. Citral, Citronellol, d-Limonene, Geraniol and Linalool may cause allergic reactions.

CURECEE contains glucose (150mg per lozenge) and lactose (50mg per lozenge). This should be taken into account in patients with diabetes mellitus. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption insufficiency should not take this medicine.

This medicine contains sulphites – Sulphur dioxide (E220) which may rarely cause severe hypersensitivity reactions and bronchospasm.

This medicine contains colouring agents (Scaret red and Sunset Yellow), which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Although certain medicines should not be used together at all, in other cases two different medicines may be used together even if an interaction might occur. In these cases, your doctor may want to change the dose, or other precautions may be necessary. When you are receiving this dietary supplement, it is especially important that your health care professional know if you are taking any of the medicines listed below. The following interactions have been selected on the basis of their potential significance and are not necessarily all-inclusive.

Using CURECEE dietary supplement with any of the following medicines is usually not recommended, but may be required in some cases. If both medicines are prescribed together, your doctor may change the dose or how often you use one or both of the medicines.

- ✧ Amygdalin
- ✧ Deferoxamine

Using CURECEE dietary supplement with any of the following medicines may cause an increased risk of certain side effects, but using both drugs may be the best treatment for you. If both medicines are prescribed together, your doctor may change the dose or how often you use one or both of the medicines.

Indinavir

Interactions with food/tobacco/alcohol

Certain medicines should not be used at or around the time of eating food or eating certain types of food since interactions may occur. Using alcohol or tobacco with certain medicines may also cause interactions to occur. Discuss with your health care professional the use of your medicine with food, alcohol, or tobacco.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of amylmetacresol, 2,4-dichlorbenzyl alcohol and ascorbic acid (CURECEE).

As with all medicines care should be taken when using this product in pregnancy and medical advice sought if necessary.

Breast-feeding

(CURECEE)Ascorbic acid or metabolites are excreted in human milk, but at therapeutic doses of the product no effects on breastfed newborns / infants are anticipated. It is unknown whether 2,4-dichlorobenzyl alcohol, amylmetacresol or metabolites are excreted in human milk. A risk to the newborns / infants cannot be excluded.

Fertility

No data are available regarding the effects on fertility.

4.7 Effects on ability to drive and use machines

No or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The list of the following adverse effects relates to those experienced with 2,4-dichlorobenzyl alcohol and amylmetacresol at OTC doses, in short term use..

Adverse events which have been associated with 2,4-dichlorobenzyl alcohol and amylmetacresol are given below, tabulated by system organ class and frequency. Frequencies are defined as: Very common (≥1/10); Common (≥1/100 and <1/10); Uncommon (≥1/1000 and <1/100); Rare (≥1/10,000 and <1/1000); Very rare (<1/10,000); Not known (cannot be estimated from the available data). Within each frequency grouping, adverse events are presented in order of decreasing seriousness.

System Organ Class	Frequency	Adverse Events
Immune System Disorders	Not known	Hypersensitivityab1
Gastrointestinal Disorders	Not known	Glossodyniaab, oral discomfortab

a2,4-dichlorobenzyl alcohol bamylmetacresol

1 Hypersensitivity reactions may include rash, urticaria and angioedema, which may include swelling of the face, neck, throat or tongue that could affect breathing.

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. Health care professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Overdosage should not present a problem other than gastrointestinal discomfort.

Treatment should be symptomatic.

Frequently eating foods high in vitamin C should not lead to any health issues. Taking too much CURECEE through supplements can, however, cause side effects.

In adults, the recommended dietary allowance (RDA)Trusted Source of vitamin C is 90 milligrams (mg) for males and 75 mg for females.

Adults who take more than 2,000 mg of CURECEE per day may experience side effects.

When a person takes more than the recommended limit of CURECEE, they may experience mild digestive disturbances. These can occur if the CURECEE that the body does not absorb irritates the gastrointestinal tract.

Common mild side effects of too much vitamin C include:

diarrhea

nausea

stomach cramping

bloating

general abdominal discomfort

The body does not absorb all of the CURECEE that it gets from supplements.

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5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Throat Preparations; Antiseptics**; ATC Code:** R02AA03 Dichlorobenzyl alcohol.

2,4-Dichlorobenzyl alcohol and amylmetacresol have antiseptic properties.

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

5.2 Pharmacokinetic properties

Oral ingestion of food or supplements is the primary route of administration for CURECEE. Vitamin C is ubiquitous in nature and particularly fruits and vegetables contain relatively large amounts of ASC . For healthy individuals, it is possible to get sufficient amounts of CURECEE through the diet provided it contains high amounts of vitamin C-rich sources.

Absorption

Vitamin C exists primarily in two forms in vivo, ASC (reduced form) and DHA (oxidized form), of which the former is by far the predominant . Due to the efficient intracellular recycling of DHA to ASC by most cell types, the total available vitC capacity is considered the combined pool of ASC and DHA . With regard to CURECEE, three potential modes of membrane transport exist: passive diffusion, facilitated diffusion, and active transport. However, vitamin C is predominantly represented by its anionic form (>99.9%) at neutral pH and is highly water-soluble. As such, it will only be able to diffuse across the plasma membrane at a relatively slow rate even in the presence of a considerable concentration gradient. However, in the milieu of the stomach (pH 1) or small intestine (pH 5), the proportion of unionized Ascorbic acid increases to 99.9% and 15%, respectively, and under these local conditions, passive diffusion could perhaps play a more significant role in vitamin C uptake.

Distribution

The distribution of vitC is highly compartmentalized . Simple diffusion is unlikely to play a major role in vitC transport across membranes, at least in the further distribution from the blood stream. From a theoretical point of view, ASC plasma steady state concentrations would be 2.5-fold higher than in tissue as calculated by a dissociation-determined equilibrium. In reality, intracellular concentrations of ASC range from about 0.5 to 10 mM compared to the mere 50–80 μM in the plasma of healthy individuals , confirming a many-fold preference for tissue. Although the glucose transporters (GLUTs 1–4 and 8) capable of facilitating diffusion of DHA are widely represented throughout the body [31,32,41,42,43], the negligible amount of oxidized vitamin C present in plasma of healthy individuals precludes that GLUT mediated transport per se is of major importance in the diverse distribution of vitamin C. One apparent exception is erythrocytes that do not contain SVCTs but are only able to take up vitamin C through facilitated diffusion . Human erythrocytes are able to recycle DHA to ASC and maintain an intracellular vitC concentration similar to that of plasma . It has been estimated that the erythrocytes alone are capable of reducing the total amount of vitamin C present in blood approximately once every 3 min . Consequently, the recycling capacity of the erythrocytes may constitute a substantial antioxidant reserve in vivo. Recent investigations actually suggest that ASC is necessary for the structural integrity of the erythrocytes and that intracellular erythrocyte ASC is essential to maintain ASC plasma concentrations in vivo . However, collectively speaking and considering the quantitative importance of mechanisms, ASC is primarily distributed via active transport.

Metabolism

In contrast to plants, where a number of ASC derivatives and analogues, including several glucosides, have been identified, only ASC exists in mammals . The metabolism of ASC is intimately linked to its antioxidant function. Through its enediol structure that is highly resonance stabilized and influenced by the acidity of the molecule, ASC serves as an efficient electron donor in biological reactions. In supplying reducing equivalents as either a cofactor or free radical quencher, ASC itself is oxidized to the comparatively stable radical intermediate, ascorbyl free radical, two molecules of which may be disproportionate at a physiological pH to one molecule of ASC and one of DHA. As mentioned earlier, DHA is efficiently reduced intracellularly by a number of cell types, thereby preserving the ASC pool. Turnover of vitamin C is therefore particularly linked to the catabolism of DHA which occurs through hydrolysis to 2,3-diketogulonic acid and decarboxylation to l-xylonate and l-lyxonate, both of which can enter the pentose phosphate pathway for further degradation’

Excretion and Reuptake

As a highly hydrophilic low molecular weight compound, ASC would be expected to be efficiently excreted through the kidneys. Indeed, ASC is quantitatively filtered through glomerulus by means of the hydrostatic pressure gradient and concentrated in the pre-urine subsequently to the resorption of water. Here, the pH drops to about five, resulting in an increased proportion of unionized ascorbic acid to that of ASC. The ascorbic acid increase from <0.01% in plasma to about 15% in the pre-urine, representing a concentration gradient of 1500:1, would for most molecules result in substantial passive reabsorption but does apparently not occur for ascorbic acid presumably due to its low lipid solubility. Instead, reuptake of ASC in the proximal renal tubules is controlled by saturable active transport through SVCT1. However, for individuals with saturated plasma levels, excretion of surplus vitC is quantitative.

The importance of SVCT1 for intestinal vitC uptake and, in particular, for renal reuptake has been illustrated by Corpe et al. who showed that Slc23a1-/- mice display an 18-fold increased excretion of ASC, lower body pool and vitC homeostasis, and increased mortality. They also modelled the effect of known human polymorphisms in the SVCT1 on the plasma saturation level and came to the astonishing conclusion that the most severely affected SNP (A772G rs35817838) would result in a maximal plasma concentration of less than 20 μM , i.e., a potential life-long state of vitC deficiency regardless of intake. The renal reuptake of ASC is highly concentration-dependent. Levine and coworkers have shown in detail that the renal excretion coefficient of ASC ranges from 0 to 1 depending on the individual’s vitC status, i.e., corresponding to quantitative reuptake in individuals with poor vitC status and quantitative excretion in individuals with saturated status . The fact that the excretion ratio is about 1 for intakes higher than about 500 mg/day in healthy individuals supports that passive reabsorption of vitC does not play a significant role in the kidneys.

Distribution

measured ASC concentrations in tumor tissue following high-dose vitC administration in a mouse model and found that daily injections were necessary to delay tumor growth and suppress the transcription factor hypoxia-inducible factor 1. Interestingly, it was also found that elimination was significantly delayed in tumor compared to normal tissue , which may help in preserving the effect of ASC in tumors between infusions. In an attempt to mimic tissue diffusion rates and availability in both normal and tumor tissue, Kuiper and coworkers used a multicell-layered, three-dimensional pharmacokinetic model to measure ASC diffusion and transport parameters through dense tissue in vitro.

They were able to simulate diffusion under a number of conditions, including tumors, and concluded that supraphysiological concentrations of ASC, achievable only by intravenous infusion, are necessary for effective delivery of ASC into poorly vascularized tumors. Using these data, it was recently rationalized that normal body saturation obtained by adequate oral dosing will be able to diffuse to cover the distance between vessels in normal well-perfused tissue, and thus provide sufficient vitC for the entire body. In contrast, this diffusion distance is insufficient to increase the vitC content of tumors with poor vascularization, which requires above millimolar concentrations plasma concentrations for effective vitC diffusion. Other than that, very little is known about the organ and tissue homeostasis following intravenous infusion of high-dose vitC.

Metabolism and Excretion

Following high-dose intravenous administration of vitC, the dose-dependency of the elimination phase, as evident at levels below saturation as described above, is surpassed. VitC is quickly eliminated through glomerular filtration with no significant reuptake. This renders the half-life constant and the elimination kinetics first order. Several pharmacokinetic studies of high-dose vitC have calculated a constant elimination half-life of about 2 h following the discontinuation of intravenous infusion . This suggests that the millimolar plasma concentrations achieved by intravenous infusion are normalized to physiological levels in about 16 h. In this perspective, the observation that tumor tissue may maintain an elevated level for as much as 48 h is interesting , and may be mediated by increased stability in the hypoxic tumor environment, but most likely also by the delayed clearance due to poor vascularization.

5.3 Preclinical safety data

None available.

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6. Pharmaceutical particulars

6.1 List of excipients

Sugar

Lactose

Tartaric acid

Ethanol

Sunset Yellow

Carmine

Scaret red

Dextrin

Aspertame

Lemon flavor

Magnesium Stearate

Talc powder

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

The tray contains an appropriate number of lozenges to give pack sizes of 24 lozenges in a small.

6.6 Special precautions for disposal and other handling

Not applicable.

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7. Marketing authorisation holder

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8. SUPPLIER

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