## 1. PRODUCT NAME

**For 2 mg:**

SKIIP Nicotine Mini Lozenge, 2 mg (Mint flavour)

SKIIP Nicotine Mini Lozenge, 2 mg (Cinnamon flavour)

SKIIP Nicotine Mini Lozenge, 2 mg (Cherry flavour)

**For 4 mg:**

SKIIP Nicotine Mini Lozenge, 4 mg (Mint flavour)

SKIIP Nicotine Mini Lozenge, 4 mg (Cinnamon flavour)

SKIIP Nicotine Mini Lozenge, 4 mg (Cherry flavour)

## 2. DOSAGE FORMS AND STRENGTHS

**For 2 mg:**

Each lozenge contains 2 mg nicotine (as nicotine polacrilex)

**For 4 mg:**

Each lozenge contains 4 mg nicotine (as nicotine polacrilex)

## 3. PHARMACEUTICAL FORM

**For 2 mg:**

**2 mg Mini Lozenge (Mint flavour):**

White to off white oval shaped lozenges debossed with "A516” on one side and plain on other side.

**2 mg Mini Lozenge (Cinnamon flavour):**

White to off white oval shaped lozenges debossed with "A503” on one side and plain on other side.

**2 mg Mini Lozenge (Cherry flavour):**

White to off white oval shaped lozenges debossed with "A501” on one side and plain on other side.

**For 4 mg:**

**4 mg Mini Lozenge (Mint flavour):**

White to off white oval shaped lozenges debossed with "A435" on one side and plain on other side.

**4 mg Mini Lozenge (Cinnamon flavour):**

White to off white oval shaped lozenges debossed with "A421" on one side and plain on other side.

**4 mg Mini Lozenge (Cherry flavour):**

White to off white oval shaped lozenges debossed with "A415" on one side and plain on other side.

For excipients, see PHARMACEUTICAL INFORMATION – List of Excipients.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

SKIIP Nicotine Mini Lozenges are indicated for the relief of withdrawal symptoms including cravings associated with smoking cessation.

SKIIP Nicotine Mini Lozenge should preferably be used in conjunction with a behavioural support programme.

SKIIP Nicotine Mini Lozenges are indicated in adults aged 18 years and over.

### 4.2 Posology and Method of Administration

**Directions for Use**

One lozenge should be placed in the mouth and allowed to dissolve. Periodically, the lozenge should be moved from one side of the mouth to the other and repeated, until the lozenge is completely dissolved (approximately 10 – 13 minutes). The lozenge should not be chewed or swallowed whole.

Users should not eat or drink while a lozenge is in the mouth.

**Adults (18 years and over including the elderly)**

**Abrupt Cessation of Smoking**

SKIIP Nicotine Mini Lozenges, 2 mg: suitable for smokers who have their time to first cigarette is more than 30 minutes after waking up.

SKIIP Nicotine Mini Lozenges, 4 mg: suitable for smokers who have their time to first cigarette is less than 30 minutes after waking up.

Users should make every effort to stop smoking completely during treatment with SKIIP Nicotine Mini Lozenges, 2 mg and 4 mg.

Behavioural therapy, advice and support will normally improve the success rate. Users should follow the schedule of treatment below:

**Table 1:**

| **Step 1**<br>**Weeks 1 to 6** | **Step 2**<br>**Weeks 7 to 9** | **Step 3**<br>**Weeks 10 to 12** | To help stay smoke free over the next 12 weeks: take a lozenge in situations when strongly tempted to smoke. |
|---|---|---|---|
| Initial treatment period | Step down treatment period | Step down treatment period | |
| 1 lozenge every 1 to 2 hours | 1 lozenge every 2 to 4 hours | 1 lozenge every 4 to 8 hours | |

During weeks 1 to 6 it is recommended that users take at least nine lozenges per day.

Users should not exceed 20 of the SKIIP Nicotine Mini Lozenges, 2 mg or 4 mg per day during weeks 1 to 6.

Users should not use more than 1 lozenge per hour.

Those who use the lozenges beyond 6 months are recommended to seek additional help and advice from a healthcare professional.

**Gradual cessation of smoking (Reduce to quit)**

For smokers who are unwilling or unable to quit abruptly. Use a lozenge whenever there is a strong urge to smoke in order to reduce the number of cigarettes smoked as far as possible and to refrain from smoking as long as possible. The number of lozenges a day is variable and depends on the patient's needs. Nonetheless it should not exceed 20 of 2 mg or 4 mg lozenges per day.

If a reduction in cigarette consumption has not been achieved after 6 weeks of treatment, a healthcare professional should be consulted. Reduced tobacco consumption may help to lead to complete cessation of smoking. This should be attempted as soon as possible. When the number

of cigarettes has been reduced to a level from which the user feels able to quit completely, then start on the schedule for “abrupt cessation” as given above.
If an attempt to stop smoking completely has not been started within 6 months after the beginning of treatment, it is recommended to consult a healthcare professional.

**Children and adolescents**
Do not use in children and adolescents.

**4.3 Contraindications**
SKIIP Nicotine Mini Lozenge should not be used by:

- Non-smokers
- Children and adolescents (17 years and below)
- Those with hypersensitivity to nicotine or any of the excipients

**4.4 Special Warnings and Precautions for Use**
The risks associated with the use of NRT (Nicotine replacement therapy) are substantially outweighed in virtually all circumstances by the well-established dangers of continued smoking.
SKIIP Nicotine Mini Lozenge contains sucralose.
SKIIP Nicotine Mini Lozenge, 2 mg (Cherry and Mint) contains 3.22 g mannitol per 20 lozenges.
SKIIP Nicotine Mini Lozenge, 2 mg (Cinnamon) contains 3.40 g mannitol per 20 lozenges.
SKIIP Nicotine Mini Lozenge, 4 mg (Cherry and Mint) contains 2.97 g mannitol per 20 lozenges.
SKIIP Nicotine Mini Lozenge, 4 mg (Cinnamon) contains 3.15 g mannitol per 20 lozenges.

**Patients hospitalised for myocardial infarction, severe dysrhythmia or CVA**
Patients hospitalised for myocardial infarction, severe dysrhythmia or CVA (cerebrovascular accident) who are considered to be haemodynamically unstable should be encouraged to stop smoking with non-pharmacological interventions.

If this fails, SKIIP Nicotine Mini Lozenges 2 mg or 4 mg may be considered, but as data on safety in this patient group are limited, initiation should only be under medical supervision. Once patients are discharged from hospital, they can use NRT as normal. If there is a clinically significant

increase in cardiovascular or other effects attributable to nicotine, the mini lozenges should be reduced or discontinued. Use with caution in patients with recent or unstable cardiovascular disease. In patients with unstable cardiovascular disease, do not continue NRT if patient continues to smoke.

**Diabetes mellitus**

Blood glucose levels may be more variable when stopping smoking, with or without NRT, so it is important for patients with diabetes mellitus to monitor their blood glucose levels more closely than usual when NRT is initiated as catecholamines released by nicotine can affect carbohydrate metabolism and vasoconstriction may delay/reduce insulin absorption.

**Seizures**

Potential risk and benefits of nicotine should be carefully evaluated before use in subjects taking anti-convulsant therapy or with a history of epilepsy as cases of convulsions have been reported in association with nicotine.

**Allergic reactions**

Susceptibility to angioedema and urticaria. NRT should be used with caution by patients who are susceptible to angioedema and/or urticaria.

**Phaeochromocytoma and uncontrolled hyperthyroidism**

Use with caution in patients with uncontrolled hyperthyroidism or phaeochromocytoma as nicotine causes release of catecholamines. A risk-benefit assessment should be made by an appropriate healthcare professional.

**GI disease**

Swallowed nicotine may exacerbate symptoms in patients suffering from active oesophagitis, oral or pharyngeal inflammation, gastritis and gastric or peptic ulcers. Oral NRT preparations should be used with caution in these conditions. Ulcerative stomatitis has been reported. A risk-benefit assessment should be made by an appropriate healthcare professional.

**Danger in small children**

Doses of nicotine tolerated by adult and adolescent smokers can produce severe toxicity in small children that may be fatal. Products containing nicotine should not be left where they may be misused, handled or ingested by children.

**Transferred dependence**

Transferred dependence is rare and is both less harmful and easier to break than smoking dependence.

Nicotine products should be kept out of the sight and reach of children.

**Use in hepatic impairment**

Use with caution in patients with moderate to severe hepatic impairment as the clearance of nicotine or its metabolites may be decreased with the potential for increased adverse effects. A risk-benefit assessment should be made by an appropriate healthcare professional.

**Use in renal impairment**

Use with caution in patients with severe renal impairment as the clearance of nicotine or its metabolites may be decreased with the potential for increased adverse effects. A risk-benefit assessment should be made by an appropriate healthcare professional.

**Use in the elderly**

No data available.

**Paediatric use**

Do not use in children and adolescents.

**Effects on laboratory tests**

No data available.

## 4.5 Interactions with other medicines and other forms of interactions

No clinically relevant interactions between nicotine replacement therapy and other drugs have definitely been established, however nicotine may possibly enhance the haemodynamic effects of adenosine.

Smoking cessation, with or without nicotine replacement, may alter the individual's response to concomitant medication and may require adjustment of dose.

Polycyclic aromatic hydrocarbons in tobacco smoke induce the metabolism of drugs metabolised by CYP 1A2 (and possibly by CYP 1A1). When a smoker stops this may result in a slower metabolism and a consequent rise in blood levels of such drugs.

The following drugs may require adjustment in dose at cessation of smoking:

Caffeine, theophylline, imipramine, pentazocine, tacrine, clomipramine, insulin, clozapine, olanzapine and fluvoxamine. In particular, anticonvulsants may require special monitoring and/or dosage adjustment.

Other reported effects of smoking include reduced analgesic efficacy of propoxyphene, reduced diuretic response to frusemide and altered pharmacological response to propranolol, as well as altered rates of ulcer healing with H2 antagonists. Both smoking and nicotine can increase levels of circulating cortisol and catecholamines. Dosages of nifedipine, adrenergic agonists or adrenergic blocking agents may need to be adjusted.

## 4.6 Fertility, Pregnancy and lactation

### Effects on fertility

In rats and rabbits, implantation can be delayed or inhibited by a reduction DNA synthesis that appears to be caused by nicotine. Studies have shown a decrease in litter size in rats treated with nicotine during gestation.

### Use in pregnancy – Pregnancy Category D

Smoking during pregnancy is associated with risks such as intra-uterine growth retardation, premature birth or stillbirth. Stopping smoking is the single most effective intervention for improving the health of both pregnant smoker and her baby. The earlier abstinence is achieved the better.

Ideally smoking cessation during pregnancy should be achieved without NRT. However for women unable to quit on their own, NRT should only be used on the advice of a health care professional. Nicotine is harmful to the foetus. However, the risk of using NRT to the foetus is lower than that expected with tobacco smoking, due to lower maximal plasma nicotine concentration and no additional exposure to polycyclic hydrocarbons and carbon monoxide. However, as nicotine passes to the foetus affecting breathing movements and has a dose dependent effect on placental/foetal circulation, the decision to use NRT should be made as early on in the pregnancy as possible. The aim should be to use NRT for only 2-3 months. While no data exist to support one form of NRT over another, it may be prudent to use intermittent dosing products as these usually provide a lower daily dose of nicotine than patches. However, patches may be preferred if the woman is suffering from nausea during pregnancy. If patches are used they should be removed before going to bed.

**Use in lactation**

Nicotine from smoking and NRT is found in breast milk. However the amount of nicotine the infant is exposed to from NRT is relatively small and less hazardous than the second-hand smoke they would otherwise be exposed to. Nicabate patches should not be used while breastfeeding. Intermittent dosing products such as Nicabate gums, lozenges or mini lozenges, should be used while breastfeeding and women should breast feed just before they use the product to allow as long a time as possible between NRT use and feeding.

**4.7 Effects on Ability to Drive and Use Machines**

Used as recommended there are minimal risks associated with the use of SKIIP Nicotine Mini Lozenges, 2 mg and 4 mg in driving vehicles or operating machinery. Nevertheless, one should take into consideration that smoking cessation can cause behavioural changes.

**4.8 Adverse Effects (Undesirable Effects)**

SKIIP Nicotine Mini Lozenges, 2 mg and 4 mg can cause adverse reactions similar to those associated with nicotine from tobacco. Many of the observed adverse reactions are consistent with the pharmacological effects of nicotine, which are dose dependent.

**Clinical Trial Data**

The following undesirable effects detailed in Tables 2 and 3 are nicotine related adverse events for all oral dosage forms.

Table 2 shows events which were identified from a double-blind, randomised, placebo- controlled lozenge clinical study involving 1818 patients. Adverse events reported in this study have been considered for inclusion, where the incidence in the 2 mg and 4 mg nicotine arm was higher than the corresponding placebo arm. Frequencies calculated from the study safety data.

**Table 2:**

| | |
|---|---|
| **Gastrointestinal Disorder** | |
| Very common ≥1/10 | Nausea |
| Common ≥1/100;<1/10 | vomiting, dyspepsia**, abdominal pain upper, diarrhoea, dry mouth, constipation, hiccups, stomatitis, flatulence, oral discomfort |
| **Nervous System Disorders** | |
| Common ≥1/100;<1/10 | headache*, dizziness* |
| **Psychiatric Disorders** | |
| Common ≥1/100;<1/10 | insomnia* |
| **Respiratory, Thoracic and Mediastinal Disorders** | |
| Common ≥1/100;<1/10 | pharyngitis, cough*, pharyngolaryngeal pain |

*These events may also be due to withdrawal symptoms following smoking cessation.

**Individuals with a tendency to experience indigestion may suffer initially from minor degrees of indigestion or heartburn if the 2 mg or 4 mg dose is used.

**Post Marketing**

Table 3 shows events which have been identified from post-marketing experience of oral nicotine products. Frequencies for these events cannot be estimated for oral nicotine dosage forms from the available data.

**Table 3:**

| |
|---|
| **Cardiac Disorders** |
| palpitations, tachycardia, reversible atrial fibrillation |
| **Gastrointestinal Disorder** |
| dysphagia, eructation, salivary hypersecretion |
| **General Disorders and Administration Site Conditions** |
| asthenia*, fatigue*, malaise*, influenza type illness* |
| **Immune System Disorders** |
| hypersensitivity, angioedema, urticaria, ulcerative stomatitis, and very rarely anaphylactic reactions |
| **Nervous System Disorders** |
| Tremor |
| **Psychiatric Disorders** |
| nervousness* |
| **Respiratory, Thoracic and Mediastinal Disorders** |
| dyspnoea |

*These events may also be due to withdrawal symptoms following smoking cessation.

### 4.9 Overdose

Nicotine doses that are tolerated by adult smokers during treatment may produce severe symptoms of poisoning in small children and may be fatal.

Signs and symptoms of an overdose from SKIIP Nicotine Mini Lozenges, 2 mg or 4 mg would be expected to be the same as those of acute nicotine poisoning, including pallor, cold sweat, salivation, nausea, vomiting, abdominal pain, diarrhoea, headache, dizziness, disturbed hearing and vision, tremor, mental confusion and weakness.

Prostration, hypotension, respiratory failure and convulsions may ensue with large overdoses.

**Treatment of overdose**

All nicotine intake should stop immediately and the patient should be treated symptomatically. Activated charcoal may reduce absorption of the medicine if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

## 5 PHARMACOLOGICAL PROPERTIES

Nicotine, the chief alkaloid in tobacco products, binds stereoselectively to acetylcholine receptors at the autonomic ganglia, in the adrenal medulla, at neuromuscular junctions and in the brain. Two types of central nervous system effects are believed to be the basis of nicotine's positively reinforcing properties. A stimulating effect exerted mainly in the cortex via the locus ceruleus, produces increased alertness and cognitive performance. A "reward" effect via the "pleasure system" in the brain is exerted in the limbic system. At low doses the stimulant effects predominate, while at high doses the reward effects predominate. Intermittent intravenous administration of nicotine activates neurohormonal pathways, releasing acetylcholine, noradrenaline, dopamine, serotonin, vasopressin, beta-endorphin, growth hormone and ACTH.

### 5.1 Pharmacodynamic properties

**Mechanism of action**

The actions of nicotine in man are complex, depending on dose, rate of delivery, prevalent autonomic tone, individual variation and prior exposure (tolerance).

The cardiovascular effects of nicotine include peripheral vasoconstriction, tachycardia and elevated blood pressure. Acute and chronic tolerance to nicotine develops from smoking tobacco or ingesting nicotine preparations. Acute tolerance (a reduction in response for a given dose) develops rapidly (less than 1 hour), but at distinct rates for different physiological effects (skin temperature, heart rate, subjective effects). Withdrawal symptoms, such as cigarette craving, can be reduced in some individuals by plasma nicotine levels lower than those for smoking.

Withdrawal from nicotine in addicted individuals is characterised by craving, nervousness, restlessness, irritability, mood lability, anxiety, drowsiness, sleep disturbances, impaired

concentration, increase appetite, minor somatic complaints (headache, myalgia, constipation, fatigue) and weight gain. Nicotine toxicity is characterised by nausea, abdominal pain, vomiting, diarrhoea, diaphoresis, flushing, dizziness, disturbed hearing and vision, confusion, weakness, palpitations, altered respiration, and hypotension.

**Clinical trials**

A multicentre, double-blind, placebo-controlled, randomised, parallel group study assessed the efficacy of SKIIP Nicotine Mini Lozenges, 2 mg and 4 mg in smokers wanting to quit. These lozenges had a different formulation to that of the SKIIP Nicotine Mini Lozenges, 2 mg and 4 mg. Treatment allocation was based on time to first cigarette (TTFC). Those smoking within 30 minutes of waking were allocated to the 4 mg group (or matching placebo) and those smoking more than 30 minutes after waking were allocated to the 2 mg group (or matching placebo).

The study was undertaken in both the USA and the UK. A total of 1,818 smokers motivated to stop and aged over 18 years were randomised; 459 in the 2 mg active group, 458 in the 2 mg placebo, 450 in the 4 mg active and 451 in the 4 mg placebo.

Subjects were given clear instructions on how to suck the lozenge. Treatment instructions were to use one lozenge every 1-2 hours for the first 6 weeks, one lozenge every 2-4 hours for weeks 7-9, and one lozenge every 4-8 hours for weeks 10-12. Thereafter subjects were advised to use 1-2 lozenges per day as needed to remain abstinent. During the first six weeks, subjects were advised to use a minimum of 9 lozenges daily. At the end of 6 months subjects were told to abstain from taking the lozenge.

Six week, 3 month and 6 month, continuous, biochemically-confirmed smoking cessation rates presented by treatment group are tabulated below.

**Table 4:**

| | **2 mg lozenge** | |
|---|---|---|
| | Active<br>n=459 | Placebo<br>n=458 |
| 6 weeks | 46.0% | 29.7% |
| 3 months | 34.4% | 21.6% |
| 6 months | 24.2% | 14.4% |

**Table 5:**

| | **4 mg lozenge** | |
|---|---|---|
| | Active<br>n=450 | Placebo<br>n=451 |
| 6 weeks | 48.7% | 20.8% |
| 3 months | 35.3% | 14.0% |
| 6 months | 23.6% | 10.2% |

In a single clinical study, SKIIP Nicotine Mini Lozenges, 4 mg has been shown to attenuate cessation- related weight gain in high dependency smokers during the 12 weeks treatment period. Weight gain was reduced from a mean of 2.30 kg (range -3.6 to 7.3 kg) in placebo lozenge users to 1.27 kg (range -3.7 to 9.9 kg) in 4 mg lozenge users after 6 weeks lozenge use, and reduced from 3.40 kg (range -2.2 to 10.9 kg) in placebo users to 2.67 kg (range -4.2 to 14.5 kg) in 4 mg lozenge users after 3 months lozenge use. Weight gain rebounded to at least placebo levels after cessation of use of the lozenges in subjects continuing to abstain from smoking.

## 5.2 Pharmacokinetic properties

### Absorption

SKIIP Nicotine Mini Lozenges, 2 mg and 4 mg dissolve completely in the oral cavity and the entire amount of nicotine contained in the lozenge becomes available for buccal absorption or ingestion (swallowing). The complete dissolution of SKIIP Nicotine Mini Lozenges, 4 mg is typically achieved in approximately 10 - 13 minutes. The mean peak plasma concentrations of nicotine achieved after a single 4 mg dose are approximately 9.1 ng/mL.

### Distribution

The plasma protein binding of nicotine is low (4.9%), and the volume of distribution of nicotine is large (2.5 L/kg). The distribution of nicotine to tissue is pH dependent, with the highest concentrations of nicotine found in the brain, stomach, kidney and liver.

**Metabolism**

Nicotine is extensively metabolised to a number of metabolites, all of which are less active than the parent compound. The metabolism of nicotine primarily occurs in the liver, but also in the lung and kidney. Nicotine is metabolised primarily to cotinine but is also metabolised to nicotine N'-oxide. Cotinine has a half-life of 15-20 hours and its blood levels are 10 times higher than nicotine. Cotinine is further oxidised to trans-3'-hydroxycotinine, which is the most abundant metabolite of nicotine in the urine. Both nicotine and cotinine undergo glucuronidation.

**Excretion**

The elimination half-life of nicotine is approximately 2 hours (range 1 - 4 hours). Total clearance for nicotine ranges from approximately 62 to 89 l/hr. Non-renal clearance for nicotine is estimated to be about 75% of total clearance. Nicotine and its metabolites are excreted almost exclusively in the urine. The renal excretion of unchanged nicotine is highly dependent on urinary pH, with greater excretion occurring at acidic pH.

**5.3 Preclinical Safety Data**

The general toxicity of nicotine is well known and taken into account in the recommended posology. Nicotine was not mutagenic in appropriate assays. The results of carcinogenicity assays did not provide any clear evidence of a tumorigenic effect of nicotine. In studies in pregnant animals, nicotine showed maternal toxicity and consequential mild foetal toxicity. Additional effects included pre- and postnatal growth retardation and delays and changes in postnatal CNS development.

Effects were only noted following exposure to nicotine at levels in excess of those which will result from recommended use of SKIIP Nicotine Mini Lozenges, 2 mg and 4 mg. Effects on fertility have not been established.

Comparison of the systemic exposure necessary to elicit these adverse responses from preclinical test systems with that associated with the recommended use of SKIIP Nicotine Mini Lozenges, 2 mg and 4 mg indicate that the potential risk is low and outweighed by the demonstrable benefit of nicotine therapy in smoking cessation. However, SKIIP Nicotine Mini Lozenges, 2 mg and 4 mg should only be used by pregnant women on medical advice if other forms of treatment have failed.

**Genotoxicity**

Nicotine and cotinine were not mutagenic in the Ames Salmonella test. Nicotine induced repairable DNA damage in an E.coli test system. Nicotine was shown to be genotoxic in a test system using Chinese hamster ovary cells.

**Carcinogenicity**

Nicotine itself does not appear to be a carcinogen in laboratory animals. However, nicotine and its metabolites increased the incidence of tumours in the cheek pouches of hamsters and forestomach of F344 rats, respectively, when given in combination with tumour initiators. One study, which could not be replicated, suggested that cotinine, the primary metabolite of nicotine, may cause lymphoreticular sarcoma in the large intestine in rats.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Mannitol
Xanthan gum
Sodium alginate
Povidone
Hydroxypropyl cellulose
Sodium carbonate
Potassium bicarbonate
Acesulfame potassium
Sucralose
Peppermint Flavour
Cherry Flavour
Cinnamon Flavour
Colloidal silicon dioxide
Magnesium stearate

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

36 months

### 6.4 Storage Conditions

Store below 30°C. Protect from direct heat and sunlight. Keep out of reach of children.

Keep the lozenge in blister strip.

### 6.5 Nature and Contents of Container

Al/PVC/PE/PVDC Blisters

Pack Size: 10’s (1x10) Lozenges and 20’s (2x10) Lozenges

Not all pack sizes may be marketed.

### 6.6 Instructions for Use and handling and Disposal

No special requirements

## 7 PRODUCT REGISTRATION HOLDER

Wellesta Healthcare Sdn. Bhd.

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Jalan PJU 8/2, Damansara Perdana,

47820 Petaling Jaya, Selangor,

Malaysia

## 8 DATE OF REVISION

20 December 2024