SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Nicovel Mint 2 mg oromucosal powder in pouch.
Nicovel Mint 4 mg oromucosal powder in pouch.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Nicovel Mint 2 mg: One pouch contains 2 mg nicotine.
Nicovel Mint 4 mg: One pouch contains 4 mg nicotine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Oromucosal powder in pouch
Rectangular pouch filled with powder.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Nicovel Mint oromucosal powder in pouch is indicated in adults for the treatment of tobacco dependence by relieving nicotine craving and withdrawal symptoms. Nicovel Mint facilitates smoking cessation in smokers who are motivated to quit and facilitates smoking reduction in smokers who are not able or willing to quit smoking. Nicovel Mint oromucosal powder in pouch should preferably be used in conjunction with a behavioural support program.

4.2 Posology and method of administration
Posology

Adults and elderly
Initially, one pouch may be administered every 1-2 hours. The usual dosage is 8-12 pouches a day. The maximum daily dose is 24 pouches.

Smoking cessation
The duration of treatment is individual. Normally, the treatment should continue for at least 3 months. The nicotine dose should then be gradually reduced. Treatment should be discontinued when the dose has been reduced to 1-2 pouches per day. Regular use of Nicovel Mint for more than one year is generally not recommended. In some cases a longer treatment period might be necessary in order to avoid relapse. Any spare pouches should be retained, as craving may suddenly occur.

Counselling and support may increase the probability to succeed in quitting smoking.
Smoking reduction
Nicovel Mint is used between periods of smoking in order to extend the non-smoking intervals and with the objective to reduce smoking as much as possible. Professional help should be sought if a decrease in number of cigarettes per day has not been achieved after 6 weeks of treatment.

An attempt to quit smoking should be made as soon as the smoker is motivated, however no later than 6 months after treatment start. Professional help should be sought if it is not possible to make a serious attempt to quit smoking within 9 months after treatment start. Regular use of Nicovel Mint for more than 1 year is generally not recommended. Some ex-smokers may need treatment for a longer period in order to avoid relapse. Any spare pouches should be retained, as craving may suddenly occur.

Renal and hepatic impairment
See section 4.4.

Paediatric population
The safety and efficacy of Nicovel Mint in children and adolescents below 18 years of age has not been established. Nicovel Mint should not be administered to adolescents below 18 years of age without recommendation from a physician.

Method of administration
The user should not eat or drink while using the pouch. Liquids that decrease the pH in the oral cavity, e.g. coffee, fruit juice or sodas, may reduce the buccal absorption of nicotine. To achieve maximum absorption of nicotine, these liquids should be avoided for up to 15 minutes prior to using the pouch.

One pouch is placed under the upper lip for 30 minutes. In order to increase the release of nicotine the pouch can occasionally be moved around with the tongue.

4.3 Contraindications
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Recent myocardial infarction (within 3 months).
- Unstable or progressive angina pectoris.
- Prinzmetal’s variant angina.
- Severe cardiac arrhythmias.
- Stroke in acute phase.

4.4 Special warnings and precautions for use
The benefits of quitting smoking usually outweigh any risk associated with correctly administered nicotine replacement therapy (NRT).

A risk-benefit assessment should be made by an appropriate healthcare professional for patients with the following conditions:
- Cardiovascular disease: Dependent smokers with a recent myocardial infarction, unstable or worsening angina including Prinzmetal’s angina, severe cardiac arrhythmias, recent cerebrovascular accident and/or who suffer with uncontrolled hypertension should be encouraged to stop smoking with non-pharmacological interventions (such as counselling). If this fails, Nicovel Mint may be considered but as data on safety in this patient group are limited, initiation should only be under close medical supervision.
- Allergic reactions: Susceptibility to angioedema and urticaria.
• Renal and hepatic impairment: Use with caution in patients with moderate to severe hepatic impairment and/or severe renal impairment as the clearance of nicotine or its metabolites may be decreased with the potential for increased adverse effects.

• Gastrointestinal Disease: Swallowed nicotine may exacerbate symptoms in patients suffering from oesophagitis, gastric or peptic ulcers and oral NRT preparations should be used with caution in these conditions.

• Phaeochromocytoma and uncontrolled hyperthyroidism: Nicotine, both from nicotine replacement therapy and from smoking, causes release of catecholamines from the adrenal medulla. Therefore Nicovel Mint should also be used with caution in patients with hyperthyroidism or phaeochromocytoma.

• Diabetes Mellitus. Patients with diabetes mellitus should be advised to monitor their blood sugar levels more closely than usual when smoking is stopped and NRT is initiated as reduction in nicotine-induced catecholamine release can affect carbohydrate metabolism.

Continued nicotine dependence may occur but to a lower extent. The use of nicotine itself is however less harmful than smoking/use of tobacco.

Paediatric population
Danger in children: Doses of nicotine tolerated by smokers can produce severe toxicity in children that may be fatal. Products containing nicotine should not be left where they may be handled or ingested by children, see section 4.9 Overdose.

4.5 Interaction with other medicinal products and other forms of interaction

Smoking, (but not nicotine), is associated with increased activity of CYP1A2. After smoking cessation, clearance may be reduced for certain medicines that are metabolised via CYP1A2. This may lead to an increase in plasma levels for some medicinal products. The increase may have a potential clinical importance for products with a narrow therapeutic window, e.g. theophylline, tacrine, clozapine, and ropinirole.

The plasma levels of other drugs partly metabolised via CYP1A2 e.g. imipramine, olanzapine, clomipramine and fluvoxamine may also increase on cessation of smoking. Data to support this are however lacking and the possible clinical significance of this effect for these drugs is unknown.

Limited data indicate that the metabolism of flecainide and pentazocine may also be induced by smoking.

4.6 Fertility, pregnancy and lactation

Pregnancy
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 the pregnant smoker and her baby. The earlier abstinence is achieved the better.

Nicotine passes to the foetus and affects its breathing movements and circulation. The effect on the circulation is dose-dependent.

The pregnant smoker should therefore always be advised to stop smoking completely without use of nicotine replacement therapy. The risk of continued smoking may pose greater hazard to the foetus compared with the use of nicotine replacement products in a supervised smoking cessation programme. Use of Nicovel Mint by the pregnant smokers should only be initiated after advice from a health care professional.
Lactation
Nicotine passes freely into breast milk in quantities that may affect the child even with therapeutic doses. Nicovel Mint should therefore be avoided during breast-feeding.
Should smoking withdrawal not be achieved, use of Nicovel Mint by breast feeding smokers should only be initiated after advice from a health care professional. If nicotine replacement therapy is used whilst breast-feeding Nicovel Mint should be taken immediately after breast feeding and not within two hours before breast feeding.

Fertility
Smoking increases the risk for infertility in woman and men. In vitro studies have shown that nicotine can adversely affect human sperm quality. In rats, impaired sperm quality and reduced fertility have been shown.

4.7 Effects on ability to drive and use machines
Nicovel Mint has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects
Nicovel Mint may cause adverse events similar to those associated with nicotine administered by other means. The adverse events are dose dependent. Most adverse events reported by patients usually occur during the first 3-4 weeks after treatment start.

Frequency of adverse events according to MedDRA-system organ class database.
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); very rare (<1/10 000), not known (cannot be estimated from the available data).

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Undesirable effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Dizziness, headache</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Palpitations</td>
</tr>
<tr>
<td>Rare</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Gastrointestinal discomfort, hiccups, nausea, vomiting.</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Erythema, hives</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Irritated mouth or throat</td>
</tr>
<tr>
<td>Rare</td>
<td>Allergic reaction such as e.g. angioedema</td>
</tr>
</tbody>
</table>

Some symptoms, such as dizziness, headache and insomnia, which have been reported may be related to withdrawal symptoms associated with smoking cessation. Increased frequency of aphthous ulcers may occur when smoking is stopped. The causality is unclear.

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 the national reporting system listed in
[To be completed nationally]
4.9 Overdose

Symptoms of overdose with nicotine may occur in patients with low pre-treatment nicotine intake or if other sources of nicotine are used concomitantly.

Symptoms of overdose are those of acute nicotine poisoning and include nausea, salivation, abdominal pain, diarrhoea, sweating, headache, dizziness, disturbed hearing and pronounced weakness. At high doses, these symptoms may be followed by hypotension, weak and irregular pulse, breathing difficulties, fatigue, circulatory collapse and general convulsions.

Doses of nicotine that are tolerated by adult smokers during on-going treatment may cause severe symptoms of poisoning in small children and may prove fatal.

Management of overdose: Administration of nicotine must be stopped immediately and the patient should be treated symptomatically. Activated charcoal reduces the gastrointestinal absorption of nicotine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in nicotine dependence

ATC kod: N07BA01

Abrupt cessation of the use of tobacco-containing products following a prolonged period of daily use may result in characteristic withdrawal symptoms that include four or more of the following: dysphoria or depressed mood, insomnia, irritability, frustration or aggression, anxiety, difficulty concentrating, restlessness or impatience, decreased heart rate, increased appetite or weight gain. Nicotine craving, which is recognised as a clinically relevant symptom, is also an important element in nicotine withdrawal. Clinical studies have shown that nicotine replacement products can help smokers abstain from smoking by relieving these withdrawal symptoms.

A 6 week smoking cessation and tolerability study including 48 subjects was performed with ad libitum use of nicotine 4 mg oromucosal powder in pouch. The number of pouches used per week showed an average reduction of 56% and the total time of use was reduced by 44% compared with baseline. During the 6 week study period the number of subjects with lesions associated with smoking decreased. No subject developed any specific lesion at the site where the nicotine pouch was placed.

5.2 Pharmacokinetic properties

Absorption

The amount of released nicotine that is absorbed from a nicotine pouch depends on the amount of nicotine released in the oral cavity and the amount that is swallowed. The main part of nicotine that is released is absorbed through the buccal mucosa. The systemic bioavailability of swallowed nicotine is lower due to first- passage elimination. The high and rapidly rising nicotine concentrations observed after smoking are rarely reached after treatment with the pouch.

Maximal blood concentration is achieved after 30 minutes of use and is then comparable to the concentration, appearing 20-30 minutes after smoking a cigarette (medium strength).
Distribution
The volume of distribution following i.v. administration of nicotine is about (2-) 3 l/kg. Plasma protein binding for nicotine is less than 5%. Other diseases or concomitant use of other drugs which influence levels of plasma proteins are not expected to have any significant effect on the kinetics of nicotine.

Metabolism
Nicotine is metabolized mainly in the liver and plasma clearance is in average about 70 l/hour. Nicotine is metabolized also in kidneys and lungs. More than 20 metabolites have been identified, and all are believed to be less active than nicotine. The primary metabolite is cotinine which has a half-life of 15-20 hours and which produces approximately 10 times higher plasma concentrations than nicotine.

Elimination
The major metabolites in urine are cotinine (15 % of the dose) and trans-3-hydroxycotinin (45% of the dose). About 10% of nicotine is excreted unchanged in the urine. As much as 30% of nicotine may be excreted in the urine at increased diuresia and acidification of the urine below pH 5. The half-life of nicotine is approximately 2 hours.

Special populations
Heavily impaired kidney function is assumed to exert influence on total clearance of nicotine. The pharmacokinetics of nicotine are unaffected in cirrhotic patients with mild liver impairment (Child score 5) and decreased in liver cirrhosis patients with moderate liver impairment (Child score 7). Increased nicotine levels have been observed in smoking haemodialysis patients.

Minor reduction of total clearance of nicotine has been demonstrated in healthy, elderly users, however, adjusting of the dose is not necessary.

No differences in nicotine kinetics have been observed between males and females.

5.3 Preclinical safety data
Nicotine was positive in some in vitro genotoxicity tests but there are also negative results with the same test systems. Nicotine was negative in in vivo tests. Animal experiments have shown that nicotine exposure results in decreased birth weight, decreased litter size and decreased survival of off-spring. The results of carcinogenicity assays did not provide any clear evidence of a tumorigenic effect of nicotine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Alginic acid
Sodium carbonate, anhydrous
Copovidone
Cellulose, powdered
Peppermint flavour
Neohesperidin dihydrochalcone

6.2 Incompatibilities
Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Keep the container tightly closed in order to protect from moisture.

6.5 Nature and contents of container

20 pouches in a polypropene container with a lid in a laminated aluminium envelope. The pouch is made of non-woven fabric composed of viscose and an acrylic binder.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHOURISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

29 June 2017