SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cytisinicline 1.5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1.5 mg of cytisinicline (previously used name: cytisine).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Round, biconvex, white tablet with diameter 6 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Smoking cessation and reduction of nicotine cravings in smokers who are willing to stop smoking.
The treatment goal of Cytisinicline is the permanent cessation of the nicotine-containing products use.

4.2 Posology and method of administration

Posology
One package of Cytisinicline (100 tablets) is sufficient for a complete treatment course.
The duration of therapy is 25 days.

Cytisinicline should be taken according to the following schedule:

Days of treatment	Recommended dosing	Maximum daily dose
From the 1st to the 3rd day	1 tablet every 2 hours	6 tablets
From the 4th to the 12th day	1 tablet every 2.5 hours	5 tablets
From the 13th to the 16th day	1 tablet every 3 hours	4 tablets
From the 17th to the 20th day	1 tablet every 5 hours	3 tablets
From the 21st to the 25th day	1-2 tablets a day	to 2 tablets

Smoking should be stopped no later than on the 5th day of treatment. Smoking should not be continued during treatment as this may aggravate adverse reactions (see section 4.4). In case of treatment failure, the treatment should be discontinued and may be resumed after 2 to 3 months.

Special population (renal impairment, hepatic impairment)
There is no clinical experience of Cytisinicline in patients with renal or hepatic impairment, therefore the drug product is not recommended for use in this patient population.

Elderly population
Due to limited clinical experience, Cytisinicline is not recommended for use in elderly patients over 65 years of age.

Paediatric population

The safety and efficacy of Cytisinicline in persons under 18 years of age have not been established. Cytisinicline is not recommended for use in persons under 18 years of age.

Method of administration

Cytisinicline should be taken orally with a suitable amount of water.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1,
Unstable angina,
A history of recent myocardial infarction,
Clinically significant arrhythmias,
A history of recent stroke,
Pregnancy and breastfeeding.

4.4 Special warnings and precautions for use

Cytisinicline should be taken only by those with a serious intention of weaning off nicotine. Patient should be aware, that the simultaneous administration of the drug and smoking or use of products containing nicotine could lead to aggravated adverse reactions of nicotine.
Cytisinicline should be taken with caution in case of ischemic heart disease, heart failure, hypertension, pheochromocytoma, atherosclerosis and other peripheral vascular diseases, gastric and duodenal ulcer, gastroesophageal reflux disease, hyperthyroidism, diabetes and schizophrenia.

Effect of smoking cessation: Polycyclic aromatic hydrocarbons in tobacco smoke induce the metabolism of drugs metabolised by CYP 1A2 (and possibly by CYP 1A1). When a smoker stops smoking, this may result in slower metabolism and a consequent rise in blood levels of such drugs. This is of potential clinical importance for products with a narrow therapeutic window, e.g. theophylline, tacrine, clozapine and ropinirole.
The plasma concentration of other medicinal products metabolised in part by CYP1A2 e.g. imipramine, olanzapine, clomipramine and fluvoxamine may also increase on cessation of smoking, although data to support this are 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.

Depressed mood, rarely including suicidal ideation and suicide attempt, may be a symptom of nicotine withdrawal. Clinicians should be aware of the possible emergence of serious neuropsychiatric symptoms in patients attempting to quit smoking with or without treatment.
History of psychiatric disorders Smoking cessation, with or without pharmacotherapy, has been associated with exacerbation of underlying psychiatric illness (e.g. depression).
Care should be taken with patients with a history of psychiatric illness and patients should be advised accordingly.

Women of childbearing potential
Women of childbearing potential must use highly effective contraception while taking Cytisinicline (see section 4.5 and 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

Cytisinicline should not be used with anti-tuberculosis drugs. No other clinical data on significant interaction with other drugs.

Patient should be aware, that the simultaneous administration of the drug and smoking or use of products containing nicotine could lead to aggravated adverse reactions of nicotine (see section 4.4).

Hormonal contraceptives

It is currently unknown whether Cytisinicline may reduce the effectiveness of systemically acting hormonal contraceptives, and therefore women using systemically acting hormonal contraceptives should add a second barrier method.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of cytisinicline in pregnant women.
Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).
Cytisinicline is contraindicated during pregnancy (see section 4.3).

Breastfeeding
Cytisinicline is contraindicated during breast-feeding (see section 4.3).

Fertility
No data on the effects of Cytisinicline on fertility.

Women of childbearing potential
Women of childbearing potential must use highly effective contraception while taking Cytisinicline (see section 4.5 and 4.4). Women using systemically acting hormonal contraceptives should add a second barrier method.

4.7 Effects on ability to drive and use machines

Cytisinicline has no influence on the ability to drive and use machines.

4.8 Undesirable effects

The clinical studies and previous experience with use of cytisinicline-containing product indicate a good tolerability of cytisinicline. The proportion of patients who discontinued treatment because adverse reactions was 6-15,5% and in controlled studies it was comparable to the proportion of patients who discontinued treatment in the placebo group. Mild to moderate adverse reactions have usually been observed, most frequently concerning the gastrointestinal tract. The majority of adverse reactions occurred at the beginning of the therapy and resolved during treatment. These symptoms could also be the result of smoking cessation, rather than the use of drug product.

All adverse reactions by system organ class and frequency of occurrence in clinical trials are listed below. The frequency of occurrence is defined as follows: 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).

Metabolism and nutrition disorders:
very common: change in appetite (mainly increase), weight gain

Nervous system disorders:
very common: dizziness, irritability, mood changes, anxiety, sleep disorders (insomnia, drowsiness, lethargy, abnormal dreams, nightmares), headaches
common: difficulty in concentration
uncommon: feeling of heaviness in the head, decreased libido

Eye disorders:
uncommon: lacrimation

Cardiac disorders:
very common: tachycardia
common: slow heart rate

Vascular disorders:
very common: hypertension

Respiratory, thoracic and mediastinal disorders:
uncommon: dyspnea, increased sputum

Gastrointestinal disorders:
very common: dry mouth, diarrhea, nausea, changes flavour, heartburn, constipation, vomiting, abdominal pain (especially in the upper abdomen)
common: abdominal distension, burning tongue
uncommon: excessive salivation

Skin and subcutaneous tissue disorders:
very common: rash
uncommon: sweating, decreased elasticity of the skin

Musculoskeletal and connective tissue disorders:
very common: myalgia

General disorders and administration site conditions:
very common: fatigue
common: malaise
uncommon: tiredness

Investigations:
uncommon: increase in serum transaminase levels

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: Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms of nicotine intoxication are observed in Cytisinicline overdose. Symptoms of overdose include malaise, nausea, vomiting, increased heart rate, blood pressure fluctuations, breathing disorders, visual disturbances, clonic convulsions. In all cases of overdose, standard procedure should be taken as in acute poisoning; gastric lavage should be performed and the diuresis should be controlled with infusion fluids and diuretics. The anti-epileptic drugs, acting on the cardiovascular system and stimulating the respiration may be used, if necessary. Breathing, blood pressure and heart rate should be monitored.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: drugs used in nicotine dependence, ATC code: N07BA04

The use of Cytisinicline allows for a gradual reduction of nicotine dependence by relieving withdrawal symptoms.

The active ingredient of Cytisinicline is a plant alkaloid cytisinicline (found, among others, in seeds of golden chain, genus *Laburnum*), with a chemical structure similar to nicotine. It has an effect on acetylcholine nicotinic receptors. The action of cytisinicline is similar to that of nicotine, but in general weaker. Cytisinicline competes with nicotine for the same receptors and gradually displaces nicotine due to its stronger binding. It has lower ability to stimulate nicotinic receptors, mainly $\alpha_4\beta_2$ subtype (it is their partial agonist) and less than nicotine passes into the central nervous system. It is hypothesized that in the central nervous system cytisinicline acts on the mechanism involved in nicotine dependence and on the release of neurotransmitters. It prevents nicotine-dependent full activation of the mesolimbic dopamine system and moderately increases level of dopamine in the brain, what alleviates the central symptoms of nicotine withdrawal. In the peripheral nervous system, cytisinicline stimulates and then affects the autonomic ganglia of the nervous system, causes a reflex stimulation of breathing and secretion of catecholamines from the core part of the adrenal gland, raises blood pressure and prevents peripheral symptoms of nicotine withdrawal.

5.2 Pharmacokinetic properties

Pharmacokinetics in animals:
After oral administration of labeled cytisinicline in mice at a dose of 2 mg/kg, 42% of the administered dose was absorbed. The maximum concentration of cytisinicline in the blood was reported after 120 minutes, and within 24 hours 18% of the dose was excreted in the urine. The half-life of cytisinicline, determined after intravenous administration, was 200 minutes. Nearly 1/3 of the dose administered intravenously was excreted in the urine in 24 hours and 3% of the dose within 6 hours with faeces. The highest concentrations of drug were obtained in liver, adrenal glands and kidneys. After intravenous administration, the concentration of cytisinicline in the bile was 200 times higher than in blood. Constant level of cytisinicline concentration in the blood was accomplished in two phases after its percutaneous administration to the rabbits. The first phase lasted 24 hours and the second phase for the next three days. In the first phase, the rate of absorption and the blood level of the drug were two times higher than in the second phase. The volume of distribution (Vd) in rabbits after oral and intravenous administration was 6.21 L/kg and 1.02 L/kg, respectively. After subcutaneous administration of 1 mg/kg cytisinicline to male rats, the blood concentration was 516 ng/mL, and the concentration in the brain was 145 ng/mL. The concentration in the brain was less than 30% of the concentration in the blood. In similar experiments with subcutaneously administered nicotine, the concentration of nicotine in the brain was 65% of the concentration in the blood.

Pharmacokinetics in humans:
Absorption
The pharmacokinetic properties of cytisinicline were tested after a single oral dose of the formulation containing 1.5 mg of cytisinicline in 36 healthy volunteers. After oral administration, cytisinicline was quickly absorbed from the gastrointestinal tract. The mean maximum plasma concentration of 15.55 ng/mL was achieved after a mean of 0.92 hours.
Biotransformation
Cytisinicline was slightly metabolised.
Elimination
64% of the dose was excreted unchanged in the urine within 24 hours. The mean half-life in plasma was approx. 4 hours. The mean residence time (MRT) was approx. 6 hours.

There is no data in renally and hepatically impaired patients and the influence of food on the exposure of cytisinicline is unknown.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on non-GLP studies of repeat dose toxicity, genotoxicity and toxicity to reproduction and development.
Repeat dose toxicity studies in mice, rats and dogs did not show significant toxicity in relation to haematopoiesis, gastric mucosa, kidneys, liver and other internal organs.

Cytisinicline was not genotoxic in an *in vivo* study in mice. There was no evidence of embryotoxicity of cytisinicline in rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Cellulose, microcrystalline
Magnesium stearate
Glycerol dibehenate
Hypromellose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 25°C. Store in the original package in order to protect from moisture and light.

6.5 Nature and contents of container

PVC/PCTFE/Aluminium or PVC/PE/PVDC/Aluminium blisters placed into cardboard box containing 100 tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Bonteque Consulting Ltd
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8 MARKETING AUTHORISATION NUMBER(S)

PL 51228/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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