Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Minreksav 1.5 mg/pump actuation oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose (pump actuation) delivers 0.19 ml solution which contains 1.5 mg of cytisinicline (the previously used name: cytisine).

Excipient(s) with known effect:

Each dose of medicinal product (0.19 ml) contains: 0.17 mg of ethanol, 44.87 mg of propylene glycol and 1,71 mg sodium metabisulfite.

1 ml of oral solution contains: 0.90 mg of ethanol, 237.53 mg of propylene glycol, and 8.99 mf sodium metabisulfite.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution
Colourless to yellow, clear.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Minreksav should be taken according to the following schedule:

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

Smoking should be stopped no later than on the 5th day of treatment. The person who stopped smoking must not smoke even a single cigarette. This is essential to achieve a therapeutic success. 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 Minreksav 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, Minreksav is not recommended for use in elderly patients over 65 years of age.

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

Method of administration
Minreksav should be taken orally.
Minreksav may be administered with or without water/liquid.

Pump unlocking and usage recommendations

- Remove the protective cap of the applicator.
- Position the container in a way that the pump is on top of the container.
- The pump must be primed through pressing the top of the container (pump) with index finger 5 times, until a fine dose appears. After initial priming (which is necessary only when using the product for the first time) each actuation delivers 1.5 mg cytisinicline.
- Right after priming, the nozzle will be pointed as close to the open subject's mouth as possible.
- Press the top of the dispenser once and release one dose into the mouth, avoiding the lips and contact with parts of the oral cavity.
- After usage, place the protective cup back on the applicator.

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

Minreksav 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.

Minreksav 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, renal and hepatic impairment.

Stopping smoking
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 or using nicotine-containing products 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 effective contraception while taking Minreksav (see section 4.5 and 4.6).

Ethanol, propylene glycol, sodium, sodium metabisulfite

This medicine contains 0.17 mg of alcohol (ethanol) in each dose (0.19 ml) which is equivalent to 90.00 mg/100 ml (0.09% w/v). The amount in single dose of this medicine is equivalent to less than 1 ml beer or 1 ml wine. The small amount of alcohol in this medicine will not have any noticeable effects.

This medicine contains 44.87 mg propylene glycol in each dosage (0.19 ml) which is equivalent to 237.53 mg/ml.

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

This medicine contains sodium metabisulfite. May rarely cause severe hypersensitivity reactions and bronchospasm.

4.5 Interaction with other medicinal products and other forms of interaction

Minreksav 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 Minreksav 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).
Minreksav is contraindicated during pregnancy (see section 4.3).

Breastfeeding

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

Fertility

No data on the effects of Minreksav on fertility.

Women of childbearing potential

Women of childbearing potential must use highly effective contraception while taking Minreksav (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

Minreksav has no or negligible influence on 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: headaches, irritability, sleep disorders (insomnia, drowsiness, lethargy, abnormal dreams, nightmares), mood changes, anxiety
common: dizziness, 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, abdominal pain (especially in the upper abdomen), nausea
common: vomiting, changes flavour, constipation, diarrhea, abdominal distension, burning tongue heartburn
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:
common: fatigue, 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: HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

Symptoms of nicotine intoxication are observed in Minreksav 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 Minreksav allows for a gradual reduction of nicotine dependence by relieving withdrawal symptoms.

The active ingredient of Minreksav 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 infects 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.

The excipient glycerol moisturizes the oral mucosa and prevents the feeling of dryness in the mouth.

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 cytosine is unknown.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, toxicity to reproduction and development. The therapeutic index estimated in studies in mice, rats and dogs was wide.

No cardiac disorders were revealed in guinea pigs following a single dose of cytisinicline. 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. Studies with isolated hepatic and renal cells have not revealed any significant toxicity of cytisinicline compared to nicotine, except for a more pronounced toxicity in lipid peroxidation test, which may be associated with the fact that cytisinicline is not extensively metabolised by hepatocytes.

Cytisinicline was not genotoxic in mice. There was no evidence of embryotoxicity of cytisinicline in rats. Studies in chicken embryos revealed no teratogenic effect. Embryotoxic effects were demonstrated in chicken embryos exposed to cytisinicline at maximum doses and doses higher than the maximum doses used in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Xylitol (E967)
Sodium dihydrogen phosphate dihydrate
Glycerol
Propylene glycol
Sodium metabisulfite (E223)
Liquid mint aroma (that contains: Ethanol, anhydrous , Propylene glycol (E1520), Purified water, elavouring preparations, Natural flavouring substances)
Purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months.
Shelf life after the first opening: 6 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions. Do not refrigerate or freeze.

6.5 Nature and contents of container

Round, white, HDPE snap-on multidose container with metering pump:
1) PP actuator; PE piston; polyoxymethylene insert; PP/PE snapOn; HDPE stem; stainless steel spring and ball; HDPE/PP pump housing; LDPE/ ethylene-vinyl acetate gasket; LDPE/PP diptue with PP cap.
or
2) PP actuator, insert, steam and pump housing; LDPE piston; PE snapOn; stainless steel spring and ball; silicone gasket; LDPE/PP diptue with PP cap.

Content of solution in a multidose container is 22.0 ml which corresponds to at least 100 doses.
The container is placed in the carton box.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

Profit Sylwia Gil
Ul. Wolodyjowskiego 19
Piaseczno
05-502

Poland

8 MARKETING AUTHORISATION NUMBER

PA25384/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT