CYTISINE GPO

1. Name of the medicinal product

Cytisine GPO 1.5 mg tablet

2. Qualitative and quantitative composition

Each tablet contains 1.5 mg of cytisine

3. Pharmaceutical form

Tablet

White, round, biconvex, compressed tablets, one side debossed with “C” and the other side plain

4. Clinical particulars

4.1 Therapeutic indications [1, 1. TABEX – what it is and what it is used for, p.1]

Cytisine GPO is indicated for smoking cessation.

4.2 Posology and method of administration

Cytisine GPO can be taken with or without food. [1, Taking TABEX with food and drink, p.2] The treatment is conducted in the following schedule:

One tablet (1.5 mg) every 2 hours (6 tablets per day) for 3 days, day 1 through 3

One tablet (1.5 mg) every 2.5 hours (5 tablets per day) for 9 days, day 4 through 12

One tablet (1.5 mg) every 3 hours (4 tablets per day) for 4 days, day 13 through 16

One tablet (1.5 mg) every 5 hours (3 tablets per day) for 4 days, day 17 through 20

One tablet (1.5 mg) every 6 hours (2 tablets per day) for 5 days, day 21 through 25

The smokers should reduce of the number of smoked cigarettes during the first 4 days of treatment and stop smoking on the 5th day of the treatment. [2, Investigational medicine, p.48 & 3, Investigational medicine, p.48-49]

Alternative Dosing Schedule:

Two tablet (1.5 mg x 2) 3 times daily (6 tablets per day) for 25 days [10, Conclusion & Method, p.1656-1657]

If you take higher doses of Cytisine GPO

If you take a dose higher than prescribed, you may experience nausea, increased heartrate, or difficulty breathing. Other possible effects are vomiting and enlargement of the pupils. In this case discontinue taking Cytisine GPO and consult a doctor or ask for help at the nearest hospital.

If you forget to take Cytisine GPO

If you forget to take a dose, take it as soon after you remember as possible. If it is almost time for your next dose, take it as normal and skip the dose you forgot. Do not take a double

dose to make up for the forgotten one. Continue to take your medicine as described in this leaflet. [1, 3. How to take TABEX, p.2]

Special population (renal impairment, hepatic impairment) [1, 2.Before you take TABEX, p.1-2]

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

Elderly population [1, 2.Before you take TABEX, p.2]

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

Paediatric population [1, 2.Before you take TABEX, p.2]

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

4.3 Contraindications

Do not use Cytisine GPO in the following conditions

1. Patients with known serious hypersensitivity to cytisine or any component of the formulation
2. Pregnancy and breastfeeding
3. Advanced atherosclerosis
4. Uncontrolled hypertension [4, Clinical overview: contraindications, p.1]
5. Some forms of schizophrenia
6. Pheochromocytome [9, Drug warnings, p.17]
7. Conditions connected with severe impairment of the cardiovascular system; after a recent myocardial infarction or stroke, unstable angina, abnormal heart rhythm (cardiac arrhythmia). [9, Drug warnings, p.17 & 1. Before you take TABEX, p.1]
8. Gastroesophageal reflux disease (regurgitation of gastric juice in the bottom of the oesophagus causing a burning sensation) [1, Before you take TABEX, p.1]

4.4 Special warnings and special precautions for use [1, Take special care with TABEX, p.1-2]

There is insufficient clinical experience for the safe use of Cytisine GPO and caution should be exercised in patients with:

- Coronary artery disease (poor circulation to the heart muscle)
- Heart failure (weakness of heart muscle)
- Hypertension (high blood pressure)
- Cerebrovascular diseases
- Blockage of blood vessels
- Kidney or liver diseases

- Hyperthyroidism (overactive thyroid gland)
- Ulcer disease
- Diabetes

There is also insufficient clinical experience for the safe use of Cytisine GPO in children under 18 and adults over 65 years. Administration of Cytisine GPO is not recommended in these categories of patients without prior consultation with a physician and an assessment of benefit/risk ratio.

4.5 Interaction with other medicinal products and other forms of interaction

Theoretically, an interaction with varenicline, also used in smoking cessation, is possible, given that both act at the nicotinic receptor. Studies in mice demonstrated inhibition of phenytoin and lamotrigine anticonvulsant activity by cytisine, as well as that of lacosamide, levetiracetam, and pregabalin. [4, Interactions, p.2-3]

Tell your doctor if you use drugs such as physostigmine, galanthamine, statins, drugs to lower blood pressure, or drugs for tuberculosis due to possible increased side effects with their concomitant use with cytisine. Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. [1, Taking other medicines, p.2]

4.6 Fertility, pregnancy, and lactation

In experiment assessing the effect of cytisine on the fetus of chicken, cytisine impaired closure of abdominal and thoracic walls. No evidence for skeletal malformations caused by the drug, although curved limbs in fetuses were observed. Furthermore, the histomorphological examination showed dose-dependent dystrophy (from minimal to moderate) of the cells in the heart muscle, liver, stomach, and spleen. Embriotoxicity and possible teratogenicity of cytisine were studied in rats, the results showed that cytisine was not embriotoxic or teratogenic in pre-natal and post-natal development including maternal function. However, experimental data indicate that cytisine shows a tendency to higher toxicity during the first half of embryo development observed in fetus of chicken. [5, Reproductive and developmental Toxicity, p.16]

Information regarding use in pregnancy or lactation is lacking. At 4 to 5 weeks' gestation, nicotinic receptor proteins and gene transcripts for nicotinic receptor subunits exist in the human prenatal brain, making the consequences of cytisine use during pregnancy potentially similar to that of smoking. [4, RNP Pregnancy/Lactation, p.2]

4.7 Effects on ability to drive and use machines

No evidence of adverse effects of cytisine when carrying out activities that require alertness and responsiveness. [1, Driving and using machine, p.2]

4.8 Undesirable effects

Adverse effects reported by patients treated with cytisine in some clinical trials are listed below.

Very common

Cardiovascular: tachycardia

Gastrointestinal: dry mouth and throat, abdominal pain (mainly upper), nausea

Metabolism/nutrition: appetite changes (mainly increased appetite), weight gain

Nervous: headache, irritability, sleep disturbances (insomnia, drowsiness, abnormal dreams, nightmares), mood changes, anxiety

Skeletomuscular: muscular pain

Common

Cardiovascular: increase in blood pressure, bradycardia, cold fingers

Gastrointestinal: constipation, taste changes (mainly bitter taste), vomiting, diarrhea, flatulence, burning tongue, heartburn

General: weakness, malaise

Nervous: vertigo, loss of concentration, dizziness

Skin: rash

Uncommon

Eye: lacrimation

Gastrointestinal: salivation, elevation of aminotransferases

General: fatigue

Nervous: heaviness in the head, loss of sexual interest

Respiratory/thoracic: dyspnea, increased expectoration

Skin: increased perspiration, sagging skin [8, Safety and tolerance, p.789]

Evidence supports the safety of cytisine; long periods of post-marketing surveillance exist in the European Medicines Authority database. However, dose-dependent reports of toxicity exist.

In an open-label pharmacokinetic study in healthy adults, no effects on blood pressure or respiratory rate were observed, and reported adverse effects included increased appetite, dry mouth, dream/nightmares, and irritability. Similar findings have been reported in a systematic review of the literature.

A Cochrane meta-analysis of 3 clinical trials using cytisine report a lack of significant adverse effects, with GI disorders (dyspepsia and nausea) and headache most commonly reported. Similarly, a review that included 8 clinical trials reported more adverse GI effects with cytisine than placebo (relative risk, 1.76; 95% CI, 1.28 to 2.42) but no significant safety concerns. [4, Adverse reactions, p.3]

The results from a phase 2 randomized, double-blinded, placebo-controlled trial studied in 132 smokers aged 18-65 who smoke more than 10 cigarettes per day and have a desire to quit smoking showed that most of the adverse reactions in cytisine and placebo groups were not statistically different. Except for insomnia, 8 (21.62%) were found in the cytisine group and 1 (3.85%) were in the placebo group (p-value=0.023). In addition, the study found that the less serious side effects associated with cytisine were diarrhea, abdominal distension, headache, dizziness, drowsiness and sore throat. This was not different from that in the placebo group, and symptoms resolved after discontinuation at week 4. The symptoms that occurred in the placebo group but did not occur in the cytisine group were nausea, vomiting. [2, Adverse reactions, p.60-65]

Table 1 Adverse reactions between cytisine and placebo control groups

Adverse reactions	Cytisine				Placebo				P-value
	Week 1 % (N)	Week 2 % (N)	Week 4 % (N)	Total % (N)	Week 1 % (N)	Week 2 % (N)	Week 4 % (N)	Total % (N)	
Diarrhea	2.70(1)	2.70(1)	0	5.40(2)	3.85(1)	0	0	3.85(1)	0.577
Nausea/ vomiting	0	0	0	0	3.85(1)	0	0	3.85(1)	0.292
Flatulence	2.70(1)	2.70(1)	2.70(1)	8.11(3)	7.69(2)	7.69(2)	7.69(2)	23.08(6)	0.233
Headache	2.70(1)	5.41(2)	0	8.11(3)	0	0	0	0	0.095
Dizziness	5.41(2)	5.41(2)	0	10.81(4)	7.69(2)	0	3.85(1)	11.54(3)	0.728
Drowsiness	10.81(4)	2.70(1)	0	13.51(5)	11.54(3)	0	0	11.54(3)	0.556
Insomnia	16.22(6)	5.41(2)	0	21.62(8)	0	0	3.85(1)	3.85(1)	0.023
Depression	0	2.70(1)	0	2.70(1)	3.85(1)	3.85(1)	0	11.54(2)	0.502
Dry mouth	2.70(1)	5.41(2)	0	8.11(3)	0	0	0	23.08(6)	0.233
Throat irritation	2.70(1)	0	0	2.70(1)	0	0	0	0	0.335
Sore throat	2.70(1)	2.70(1)	2.70(1)	8.11(3)	3.85(1)	3.85(1)	3.85(1)	11.54(3)	0.919
Constipation	2.70(1)	0	0	2.70(1)	0	0	0	0	0.335
Rhinorrhea	2.70(1)	0	0	2.70(1)	0	0	0	0	0.335
Paresthesia	5.41(2)	0	0	5.14(2)	0	0	0	0	0.171
Total % (N)	22	13	2	37	16	5	5	26	

In this study, adverse reactions between cytisine and placebo control groups was evaluated by laboratory examinations namely, serum creatinine (SCr) values and estimate glomerular filtration rate (eGFR) values for renal function, aspartate aminotransferase (ALT) for liver function, electrocardiogram (EKG) for cardiac effect and forced expiratory volume in one

second (FEV_1) and %peak expiratory flow rate (%PEFR) for respiratory effects. The results showed the normal values of SCr, eGFR, ALT, FEV_1 and %PEFR and no statistically significant difference in both groups before and after treatment. For EKG results, abnormal EKG was founded in two groups of volunteer but there was no statistically significant difference. The percentage of normal EKG volunteer was increased after treatment in two groups but there was no statistically significant difference.

Table 2 Serum creatinine (SCr) values between cytisine and placebo control groups

Week	Cytisine (N=48) Mean±SD (g/dL)	Placebo (N=47) Mean±SD (g/dL)	Mean Difference	95% CI of the difference	P-value
0	0.951±0.166	0.962±0.239	-0.031	-0.115 – 0.052	0.456
4	0.982±0.158	0.963±0.285	-0.001	-0.095 – 0.092	0.974

Statistical analysis: Independent Sample Test, statistically significant at α <0.05

Table 3 Estimate glomerular filtration rate (eGFR) values between cytisine and placebo control groups

Week	Cytisine (N=48) Mean±SD (L/min)	Placebo (N=47) Mean±SD (L/min)	Mean Difference	95% CI of the difference	P-value
0	99.40±14.75	101.52±22.43	-2.120	-9.839 – 5.598	0.587
4	98.55±16.33	101.46±28.54	-2.911	-12.559 – 6.537	0.542

Statistical analysis: Independent Sample Test, statistically significant at α <0.05

Table 4 Aspartate aminotransferase (ALT) values between cytisine and placebo control groups

Week	Cytisine (N=48) Mean±SD (g/dL)	Placebo (N=47) Mean±SD (g/dL)	Mean Difference	95% CI of the difference	P-value
0	33.229±25.582	34.000±25.748	-0.771	-10.632 – 9.090	0.877
4	43.104±37.991	33.042±19.363	10.062	-2.264 – 22.387	0.108

Statistical analysis: Independent Sample Test, statistically significant at α <0.05

Table 5 Electrocardiogram (EKG) findings between cytisine and placebo control groups

Week	Clinical Finding	Cytisine (N, %)	Placebo (N, %)	Odds ratio (95% CI of the difference)	P-value
0	Normal	37 (66.07)	35 (61.40)	1.224 (0.568 – 2.639)	0.606
	Abnormal	19 (33.93)	22 (38.60)		
4	Normal	38 (79.17)	33 (71.74)	1.497 (0.581 – 3.860)	0.475
	Abnormal	10 (20.83)	13 (28.26)		

Statistical analysis: Chi-Square Test statistically significant at α <0.05

Table 6 Forced expiratory volume in one second (FEV_1) values between cytisine and placebo control groups

Week	Cytisine (N=48) Mean±SD (L/min)	Placebo (N=45) Mean±SD (L/min)	Mean Difference	95% CI of the difference	P-value
0	93.979±11.216	93.933±13.131	0.046	-4.974 – 5.066	0.986
4	95.66±10.765	92.067±19.475	3.593	-2.828 – 10.028	0.269

Statistical analysis: Independent Sample Test, statistically significant at α <0.05

Table 7 %Peak expiratory flow rate (%PEFR) values between cytisine and placebo control groups

Week	Treatment group	%PEFR±SD	Mean Difference	95% CI of the difference	P-value
0	Cytisine (N=67)	93.677±15.453	0.332	-5.722 – 5.510	0.970
	Placebo (N=65)	93.783±17.140			
2	Cytisine (N=60)	100.881±18.669	2.805	-3.548 – 9.158	0.384
	Placebo (N=57)	98.076±15.824			
4	Cytisine (N=57)	113.996±75.265	18.392	-3.26 – 40.045	0.095
	Placebo (N=51)	95.604±21.503			
12	Cytisine (N=46)	101.00±16.248	3.129	-3.945 – 10.203	0.382
	Placebo (N=44)	97.87±17.519			
24	Cytisine (N=30)	98.308±25.046	0.608	-10.788 – 12.004	0.915
	Placebo (N=31)	97.700±19.135			
48	Cytisine (N=21)	99.995±21.614	4.810	-6.867 – 16.488	0.410
	Placebo (N=22)	95.185±16.013			

Statistical analysis: Independent Sample Test, statistically significant at α <0.05

Table 8 Blood pressure levels between cytisine and placebo control groups at 0, 2, 4, 12, 24, and 48 week.

Week	Blood Pressure (mmHg)	Cytisine Mean±SD (N)	Placebo Mean±SD (N)	Mean Difference	95% CI of the difference	P-value
0	SBP	126.63±13.82 (67)	127.46±16.23 (65)	-0.83	[-6.021] – 4.352	0.751
	DBP	79.36±9.68 (67)	82.14±12.67 (65)	-2.78	[-6.655] – 1.095	0.158
2	SBP	126.73±14.64 (60)	124.98±13.16 (57)	1.750	[-3.356] – 6.857	0.498
	DBP	80.12±10.85 (60)	78.49±11.16 (57)	-1.625	[-2.405] – 5.656	0.426
4	SBP	126.00±14.37 (57)	126.76±13.22 (50)	-0.760	[-6.078] – 4.558	0.777

	DBP	79.68±11.91 (57)	78.42±12.55 (50)	1.264	[-3.427] – 5.955	0.594
12	SBP	127.52±14.32 (46)	123.37±13.452 (43)	4.150	[-1.715] – 10.014	0.163
	DBP	79.15±9.698 (46)	76.72±9.156 (43)	2.431	[-1.549] – 6.411	0.228
24	SBP	129.53±15.42 (30)	123.84±15.96 (31)	5.695	[-2.350] – 13.740	0.162
	DBP	78.73±9.81 (30)	77.23±11.16 (31)	1.508	[-3.884] – 6.899	0.578
48	SBP	128.29±16.57 (21)	125.64±11.52 (22)	2.649	[-6.106] – 11.405	0.545
	DBP	81.38±10.14 (21)	79.64±6.57 (22)	1.745	[-3.492] – 6.981	0.505

There was no significant difference in blood pressure levels between cytisine and placebo control groups both before and after treatment and no volunteer had hypertension after the treatment.

Another clinical trial studied in 1,086 participants aged 18-65 who smoke at least 10 cigarettes per day and have a desire to quit smoking, who were enrolled in a phase 3, multicenter, randomized, double-blinded, placebo-controlled trial, 540 of them were randomized to receive cytisine, whereas 546 of them received nortriptyline. Those who received cytisine will be given the standard regimen of 25-day course, along with placebo from day 26 through day 90 of treatment. with placebo nortriptyline. Those who were randomized to nortriptyline will be given nortriptyline starting at 25 mg per day and titrate up by 25 mg per week toward maximal dose of 50 mg, and 75 mg per day for those who weigh ≤50 kilogram (kg), and >50 kg, respectively. [3, Adverse reactions, p.2] Some minor adverse events, including dry mouth, drowsiness, dizziness, and nausea were reported in those who received nortriptyline whereas only dry mouth and nausea were found in those who received cytisine. No dropout of volunteer from adverse effects was found during their 5 follow-up visits, including at 2 weeks, 4 weeks, 12 weeks, 24 weeks, and 52 weeks. The adverse effects observed in this clinical trial are listed below. [3, Adverse reactions, p.192]

Table 9 Adverse events of nortriptyline and cytisine

Adverse events	Nortriptyline (N=546)	Cytisine (N=540)
Dry mouth	2 (0.37%)	1 (0.19%)
Drowsiness	3 (0.55%)	0 (0.00%)
Nausea	1 (0.18%)	1 (0.19%)
Dizziness	2 (0.37%)	0 (0.00%)

4.9 Overdose

The lethal dose of cytisine in humans is still unknown. According to one quoted report in the literature of overdose and attempted suicide, intake of approximately 40–50 (60–75

mg) and 90 (135 mg) cytisine tablets did not result in fatal or serious health consequences. In another case, ingestion of 30 mg of cytisine with excessive doses of the antidepressants moclobemide, venlafaxine and mianserin also did not cause any severe or persistent health consequences. In a New Zealand-based trial two people reported that they took all 100 tablets of cytisine in 1 week and reported no adverse reactions. [7, Safety and adverse reactions/Overdose and toxicity, p.11]

Animal studies have shown that the leaves and seeds of *L. anagyroides* and related plants are toxic. A lethal dose in horses has been estimated to be 0.5 g/kg of *L. anagyroides* seedpods.

Cytisine toxicity is considered to be dose dependent, and reports of fatalities due to respiratory failure following consumption of *L. anagyroides* plant material exist.

No antidote to cytisine toxicity has been identified, and management is supportive. [4, Toxicology, p.3] Ensure that adequate decontamination has been carried out. If patient is not breathing, start artificial respiration, preferably with a demand valve resuscitator, bag-valve-mask device, or pocket mask, as trained. Perform CPR if necessary. Immediately flush contaminated eyes with gently flowing water. Do not induce vomiting. If vomiting occurs, lean patient forward or place on the left side (head-down position, if possible) to maintain an open airway and prevent aspiration. Keep patient quiet and maintain normal body temperature. Obtain medical attention.

Maintain an open airway and assist ventilation if necessary. Administer supplemental oxygen. Treat seizures, coma, hypotension, hypertension, and arrhythmias if they occur. As antidotes at overdose for cytisine one may use tranquilizers (anticonvulsive effect) and antihypertensive drugs (decrease of the blood pressure). Observe for at least 4 to 6 hours to rule out delayed toxicity, especially after skin exposure. For ingestion of intact gum, tablets, or transdermal patches, observe for a longer period (up to 12-24 hours). Mecamylamine is a specific antagonist of nicotine actions; however, it is available only in tablets, a form not suitable for a patient who is vomiting, convulsing, or hypotensive. Signs of muscarinic stimulation (e.g., bradycardia, salivation, wheezing), if they occur, may respond to atropine. [9, Antidote and emergency treatment, p.25-26]

5. Pharmacological properties

5.1 Pharmacodynamic properties

Mechanism of action

Cytisine has been classified as a selective partial agonist and binds predominantly to the $\alpha_4\beta_2$ subtype of Nicotinic Acetylcholine Receptors (nAChRs) which mediates the rewarding and reinforcing effects of nicotine. The interaction of cytisine with $\alpha_4\beta_2$ nAChRs results in the modulation of the release of mesolimbic dopamine associated with pleasure and smoking satisfaction. [7, Mechanism of anti-smoking action, *in-vitro* studies, p.5-6]

Clinical efficacy

Phase 2 clinical trial

In a phase 2 randomized, double-blinded, placebo-controlled trial conducted in 132 smokers aged 18-65 who smoke more than 10 cigarettes per day and have a desire to quit smoking for the assessment of efficacy, safety, and quality of life of cytisine. Subjects were allocated to received either cytisine or placebo for 25-day course. The smoking cessation assessment measured self-reported results and exhaled carbon monoxide level of less than 7 ppm.

The Continuous abstinence rate (CAR) at week 2, 4,12 (CAR week 2, 4, and 12) in the cytisine treatment group was significantly higher than the placebo group, 44.78%, 18.46. % (RR 2.43; 95% CI 1.36 - 4.31; p-value 0.02), 44.78%, 15.38% (RR 2.91; 95% CI 1.55 – 5.46; p-value 0.001) and 26.87%, 10.77% (RR 2.50; 95. %CI 1.12–5.57; p-value 0.02), respectively. Although the CAR at weeks 24 and 48 of the cytisine treatment group (16.42%, 9.23% (RR 1.78; 95%CI 0.70-4.53; p-value >0.05) was higher than that the placebo group (14.93%, 6.15% (RR 2.41; 95%CI 0.80-7.35; p-value >0.05) but there was no statistically significant difference. The 7-day abstinence rate preceding the 4^{th} week assessment was significantly higher in the cytisine group than that in the placebo group but rates of abstinence at 7 days prior to the evaluation at weeks 12, 24 and 48 in the cytisine group were not statistically significant higher than that in the placebo group.

There was no statistically significant difference in the initial exhaled CO levels (exhaled CO) in the cytisine and placebo-treated subjects. The cytisine-treated group had a statistically significantly different reduction than that the placebo-treated subjects. However, at weeks 24 and 48, the total expiratory carbon monoxide levels in the cytisine and placebo group were reduced from baseline, but the difference was not statistically significant.

Subjects who successfully quit smoking continued in both the cytisine and placebo groups, both groups had the same relapse rate of 66.67%. Volunteer in the cytisine group had a longer period of relapse than the placebo group, 123.89±82.34 vs 111.57±54.88 days, respectively, although the difference was not statistically significant. The effectiveness of the smoking cessation service was found at week 4 with pulmonary function tests compared to the baseline.

Volunteers treated with cytisine showed a statistically significant difference in lung function improvement: FEV_1 before and after 4 weeks of treatment was 93.98±11.216, 95.66±10.765 (p-value 0.041: 95% CI. (-3.30) – (-0.071) while the placebo-treated subjects had decreased lung function but differed not statistically. And when considering %PEFR before and after 2, 4, and 12 weeks of service, it was found that the volunteers treated with cytisine had a statistically different increase in lung function. While the volunteers treated with placebo had a statistically significant difference in lung function improvement only in week 12 compared with baseline. The expiratory carbon monoxide content of volunteers before service versus after smoking cessation at week 2,

4, 12, 24 and 48 in the cytisine and placebo groups was found to have decreased statistically significantly.

In summary, there was a statistically significant difference in cytisine's effectiveness over placebo, especially at weeks 2, 4 and 12: 44.78% vs 18.46% (RR 2.43; 95% CI 1.36 - 4.31). p-value 0.02, 44.78% vs 15.38% (RR 2.91; 95% CI 1.55 – 5.46; p-value 0.001) and 26.87% vs 10.77% (RR 2.50; 95% CI 1.12 – 5.57; p-value 0.02) respectively. [2, Synopsis, p.9-12]

Phase 3 clinical trial

A noninferiority, multicenter, randomized, double-blinded, placebo-controlled trial, involving 6 medical centers studied in 1,086 subjects who smoked at least 10 cigarettes per day, and willing to quit smoking. All of them were randomized to receive either cytisine, or nortriptyline as their smoking cessation aid. Those who received cytisine will be given the standard regimen of 25-day course, along with placebo from day 26 through day 90 of treatment with placebo nortriptyline. Those who were randomized to nortriptyline will be given nortriptyline starting at 25 mg per day, and titrate up by 25 mg per week toward maximal dose of 50 mg, and 75 mg per day for those who weigh ≤50 kilogram (kg), and >50 kg, respectively. All participants received standard counseling from registered nurses at every clinic visit.

Complete abstinence was verified by exhaled CO measurement during their 5 follow-up visits, including at week 2, 4, 12, 24, and 52. The noninferiority margin was set at 0.05.

Among 1,086 participants who were enrolled, 540 of them were randomized to receive cytisine, whereas 546 of them received nortriptyline. The average Fagerstrom test for Nicotine Dependence (FTND) score was 2.67 ±1.37. CAR of cytisine versus nortriptyline group at 2 weeks were 28.5% VS 32.8%, (p=0.127), 4 weeks (23.52% vs 29.3%, p=0.031), 12 weeks (22.2% vs 28.6%, p=0.016), 24 weeks (14.4% vs 13.2%, p=0.548), and 52 weeks (12.2% vs 9.5%, p=0.153).

In conclusion, smoking cessation with 25-day course of cytisine is not inferior to using 3-month course of nortriptyline, along with counseling, at 1-year. [3, Abstract, p.2-3]

5.2 Pharmacokinetic properties

Absorption

Bioavailability: 90–95% [7, Pharmacokinetics, p.7]

Area under the plasma concentration versus time curve from time zero to the last measurable concentration as calculated by linear trapezoidal method ($AUC_{(0\text{-}tlast)}$): 95.350 hr•ng/mL

Area under the plasma concentration versus time curve from time zero to infinity ($AUC_{(0\text{-}\infty)}$): 100.586 hr•ng/mL

Mean peak plasma concentration (C_{max}): 18.192 ng/mL

Time to maximum plasma concentration (T_{max}): 45 minutes [6, Study synopsis, p.11]

Distribution

Protein binding: No information

Volume of distribution (V_d): 87.584 L [6, Study synopsis, p.11]

Metabolism

Clearance was found to be primarily renal, with minimal or no metabolism [7, Pharmacokinetics, p.7]

Excretion

Half-life ($T_{1/2}$): ~4 hours

Clearance: 15.312 L/hr

Elimination rate: 0.180 hr^{-1} [6, Study synopsis, p.11]

5.3 Pre-clinical safety data

Single dose toxicity

The toxicity of cytisine has been reported in animals study. The LD_{50} values obtained after intravenous (iv), subcutaneous (sc), and oral (po) administration of the drug were 2.3, 13, and 13 mg/kg for male, and 3.1, 13, and 29 mg/kg for female mice, respectively. In rats (of both sexes), the LD_{50s} were 9, 11, and 38 mg/kg after intraperitoneal (ip), sc, and po administration, respectively. There was another experiment in mice; the LD_{50} values obtained after iv, ip, and oral administration of cytisine were 1.73, 9.4, and 101 mg/kg, respectively.

When cytisine was injected sc in dogs, the LD_{50} value was 4 mg/kg.

A lethal dose of seed pods of cytisine-containing Laburnum anagyroides for horse is estimated as 0.5 g/kg. The cytotoxicity of cytisine (2 mcg/ml) *in vitro* in P-diploid human embryonal lung cells was studied, HEp-2 cells of human larynx cancer and HeLa cells of human epitheloid cervix cancer. No changes in number of cells have been observed in P-lung cells, a slight activation was established in HeLa cells. Reduction in cell numbers on the first day was observed in HEp-2 cells, but this inhibition was temporary, as on the next days the numbers of cells were as in non-treated controls. It was concluded that cytisine was not cytotoxic *in vitro*. [5, Toxicology, p.13]

Repeat dose toxicity

In repeated – dose toxicity studies, cytisine was given to the rats for 30 and 90 days in dose 7.6 mg/kg and dose up to 1.35 mg/kg, respectively. It shows no changes in clinically laboratory parameters and histomorphological changes in experimental animals. When chronically applied in mice (3.3 mg/kg) for 45 days and in rats (0.45 and 0.9 mg/kg) and dogs (0.45

mg/kg) for 6 months, cytisine does not cause any changes in clinical laboratory and histomorphological parameters in animals, but some light liver dystrophic changes were observed.

Cytisine administered orally during 5 days in rats at doses of 1 or 5 mg/kg did not show ulcerogenic activity evaluated by macroscopic and histological analysis. Cytisine had more favorable safety profile with respect to the stomach mucosa in comparison with nicotine given orally at equal doses.

In rats study, cytisine was administered orally 5 mg/kg for 14 days. It did not significantly change the values of serum transaminase activity, AST and ALT, in any of the treated strains. These results might be due to the shorter period of administration (14 days) and to the large individual variations.

Cytisine increased the MDA quantity in the liver both in spontaneously hypertensive rats (SHR) and in Wistar Kyoto (WKY), by 25% and by 29% respectively. While the GSH level was not significantly changed by the compound in both strains.

There is another *in vivo* study on the potential hepatotoxic effect of cytisine in rats. It determined that chronic administration of the drug at a dose of 1.35 mg/kg during 90 days caused a 2-fold increase in blood glutamic pyruvic transferase (GPT) concentration, without significant changes in blood glutamic oxaloacetic transferase (GOT) and alkaline phosphatase.

When cytisine was administered during 180 days to dogs (0.46 mg/kg), such changes of SGOT were not observed.

In experiments assessing the effects of cytisine on the human kidney epithelial cell line HEK-293T, the drug displayed marginal cytotoxic potential. Changes in transepithelial electrical resistance are indicative of toxic effects. A measurement of transepithelial electrical resistance showed no significant alterations of this parameter upon continuous exposure of HEK-293T monolayers to cytisine. Moreover, a morphological analysis showed that the cell cultures treated with cytisine at the concentrations up to 200 μM did not differ morphologically from the untreated controls. It has been concluded that cytisine is devoid of cytotoxic effects on human kidney cells.

In contrast to hepatocytes, cytisine did not exhibit toxic effect on P-diploid human embryonal pulmonary cells, human larynx cancer cell lines HEp-2 or human epitheliod cancer cell lines HeLa. [5, Toxicology, p.14-15]

Genotoxicity

Cytisine was not genotoxic in the test for cytogenetic aberrations *in vivo* in mice bone marrow cells. When applied orally at doses of 1 mg/kg or 5 mg/kg, it did not induce statistically significant increase in frequency of cells with abnormalities as compared with the control. Only at 10 mg/kg, cytisine induced minimal, non-specific chromosomal abnormalities. In comparison

with nicotine that caused damage to DNA in epithelial cells, cytisine had much lesser clastogenic activity. Higher frequency of chromosomal aberrations was seen even at the lowest dose of nicotine (0.1 mg/kg) as compared with the 100-fold higher dose of cytisine (10 mg/kg). An analysis of the genotoxicity study did not indicate any clastogenic activity of cytisine to be risky for humans. [5, Toxicology, p.15]

Carcinogenicity

The cytotoxicity study of cytisine (2 mcg/ml) was performed *in vitro* in P-diploid human embryonal lung cells, HEp-2 cells of human larynx cancer and HeLa cells of human epitheloid cervix cancer. No changes in number of cells have been observed in P-lung cells, a slight activation was established in HeLa cells. Reduction in cell numbers on the first day was observed in HEp-2 cells, but this inhibition was temporary, as on the next days the numbers of cells were as in non-treated controls. The authors concluded that cytisine was not cytotoxic *in vitro*. As mentioned in material safety data of cytisine, no component of this product presents at levels greater than or equal to 0.1% is identified as probable, possible or confirmed human carcinogen by International Agency for Research on Cancer (IARC). [5, Toxicology, p.15]

6. Pharmaceutical particulars

6.1 List of excipients

Calcium hydrogen phosphate, pregelatinized starch, croscarmellose sodium, magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Each OPA/Al/PVC-Al blister pack contains 10 tablets, and one carton contains 10 blister packs

6.6 Special precautions for disposal and other handling

No information

7. Marketing authorization holder

The Government Pharmaceutical Organization 75/1 Rama VI Road, Ratchathewi, Bangkok, Thailand 10400.

8. Marketing authorization number

9. Date of authorization

10. Date of revision of the text

October 2023