PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

1 NAME OF THE MEDICINE

VARIMAPIX 0,5 mg film-coated tablets

VARIMAPIX 1 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

VARIMAPIX 0,5 mg: Each film-coated tablet contains 0,5 mg of varenicline (as tartrate).

VARIMAPIX 1 mg: Each film-coated tablet contains 1 mg of varenicline (as tartrate).

Sugar free.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablets.

VARIMAPIX 0,5: White to off white film-coated tablet.

VARIMAPIX 1: Light blue film-coated tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

VARIMAPIX is indicated as an aid to smoking cessation in patients committed to stop smoking, in addition to a behaviour modification programme, for 12 weeks.

4.2 Posology and method of administration

Posology

All smoking cessation therapies are more likely to succeed in patients who are motivated to stop smoking and who are provided with additional advice and continuous support.

Patients should be treated with VARIMAPIX for 12 weeks.

The recommended dose of VARIMAPIX is 1 mg twice daily following a 1-week titration as follows:

Days 1 - 3:	0,5 mg once daily in the evening
Days 4-7:	0,5 mg twice daily
Day 8 - End of treatment:	1 mg twice daily

The patient should set the date to stop smoking. VARIMAPIX dosing should start 1 - 2 weeks before this date.

Patients who do not succeed in stopping smoking during 12 weeks of initial therapy, or who relapse after treatment, should be encouraged to make another attempt once factors contributing to the failed attempt have been identified and addressed.

For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks treatment with VARIMAPIX at 1 mg twice daily may be considered for the maintenance of abstinence. A gradual approach to quitting smoking with VARIMAPIX should be considered for patients who are not able or willing to quit abruptly. Patients should reduce smoking during the first 12 weeks of treatment and quit by the end of that treatment period. Patients should then continue taking VARIMAPIX for an additional 12 weeks for a total of 24 weeks of treatment. Patients who cannot tolerate adverse reactions of VARIMAPIX may have the dose lowered temporarily or permanently.

Dose tapering of VARIMAPIX is not required at the end of treatment.

Special populations

Patients with renal insufficiency

No dosage adjustment is necessary for patients with mild (estimated creatinine clearance > 50 mL/min and ≤ 80 mL/min) to moderate (estimated creatinine clearance ≥ 30 mL/min and ≤ 50 mL/min) renal impairment.

For patients with severe renal impairment, the recommended dose of VARIMAPIX is 1 mg once daily. Dosing should begin at 0,5 mg once daily for the first 3 days then increased to 1 mg once daily (see section 5.2).

There is insufficient clinical experience with VARIMAPIX in patients with end stage renal disease.

Patients with hepatic impairment

No dosage adjustment is necessary for patients with hepatic impairment (see section 5.2).

Use in elderly patients

No dosage adjustment is necessary for elderly patients (see section 5.2). Because elderly patients are more likely to have decreased renal function, medical practitioners should consider the renal status of an elderly patient.

Paediatric population

Safety and effectiveness of VARIMAPIX in paediatric patients have not been established; therefore, VARIMAPIX is not recommended for use in patients under 18 years of age (see section 5.2).

Method of administration

For oral administration and the tablets should be swallowed whole with water.

4.3 Contraindications

- Hypersensitivity to varenicline or to any of the excipients (see section 6.1).

4.4 Special warnings and precautions for use

Effect of smoking cessation

Physiological changes resulting from smoking cessation, with or without treatment with VARIMAPIX, may alter the pharmacokinetics or pharmacodynamics of some medicines, for which dosage adjustment may be necessary (examples include theophylline, warfarin and insulin). However, in post-marketing data there were cases of increased INR. INR should be monitored more frequently, and the warfarin dose adjusted while using VARIMAPIX, and after discontinuation of VARIMAPIX (see section 4.5).

Neuropsychiatric symptoms and suicidality

Serious neuropsychiatric symptoms have been reported in patients being treated with varenicline. These post-marketing reports have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, agitation, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide (see section 4.8). Some reported cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication.

However, some of these symptoms have occurred in patients taking varenicline as contained in VARIMAPIX who continued to smoke. When symptoms were reported, most were during varenicline treatment, but some were following discontinuation of varenicline therapy. These events have occurred in patients with and without pre-existing psychiatric disease; some patients have experienced worsening of their psychiatric illnesses. All patients being treated with VARIMAPIX should be observed for neuropsychiatric symptoms or worsening of pre-existing psychiatric illness.

Advise patients and caregivers that the patient should stop taking VARIMAPIX and contact a healthcare provider immediately if agitation, depressed mood, changes in behaviour or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behaviour. In many post-marketing cases, resolution of symptoms after discontinuation of varenicline as contained in VARIMAPIX was reported, although in some cases the symptoms persisted, therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

Medical practitioners should be aware of the possible emergence of serious neuropsychiatric symptoms in patients attempting to quit smoking with or without treatment. If serious neuropsychiatric symptoms occur whilst on VARIMAPIX, patients should discontinue VARIMAPIX immediately and contact a medical practitioner for reevaluation of treatment.

Seizures

In clinical trials and post-marketing experience there have been reports of seizures in patients with or without a history of seizures, treated with varenicline as contained in VARIMAPIX. VARIMAPIX should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Treatment discontinuation

At the end of treatment, discontinuation of varenicline as contained in VARIMAPIX was associated with an increase in irritability, urge to smoke, depression, and/or insomnia in up to 3 % of patients.

Angioedema and hypersensitivity reactions:

There have been post-marketing reports of hypersensitivity reactions including

angioedema in patients treated with varenicline (see section 4.8). Clinical signs included swelling of the face, mouth (tongue, lips, and gums), extremities, and neck (throat and larynx). There were infrequent reports of life-threatening angioedema requiring urgent medical attention due to respiratory compromise. Patients should be instructed to discontinue VARIMAPIX and immediately seek medical care if they experience these symptoms.

Serious skin reactions

There have been post-marketing reports of serious skin reactions, including Stevens-Johnson Syndrome and Erythema Multiforme in patients using varenicline as contained in VARIMAPIX (see section 4.8). As these skin reactions can be life-threatening, patients should be instructed to stop taking VARIMAPIX and contact their healthcare provider immediately at the first appearance of a skin rash with mucosa! lesions or any other signs of hypersensitivity.

Cardiovascular effects

ln a smoking cessation trial of patients with stable cardiovascular disease, cardiovascular events were reported more frequently in patients treated with varenicline as contained in VARIMAPIX. A meta-analysis of 15 clinical trials, which included the smoking cessation trial of patients with stable cardiovascular disease, had similar results. Cardiovascular events occurred primarily in patients with known cardiovascular disease. Patients should be instructed to notify their healthcare professionals of new or worsening cardiovascular symptoms and to seek immediate medical attention if they experience signs and symptoms of myocardial infarction or stroke.

VARIMAPIX contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicines and other forms of interaction

Based on varenicline characteristics and clinical experience to date, VARIMAPIX has no clinically meaningful interactions.

No dosage adjustment of VARIMAPIX or co-administered medicines listed below is recommended.

*In vitro s*tudies demonstrate that varenicline (as in VARIMAPIX) does not inhibit cytochrome P450 enzymes (IC50 > 6 400 ng/ml). The P450 enzymes tested for inhibition were: 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4/5. Also, in human hepatocytes *in vitro*, varenicline was shown to not induce the activity of cytochrome P450 enzymes 1A2 and 3A4. Therefore, VARIMAPIX is unlikely to alter the pharmacokinetics of compounds that are primarily metabolised by cytochrome P450 enzymes.

In vitro studies demonstrate that varenicline does not inhibit human renal transport proteins at therapeutic concentrations. Therefore, medicines that are cleared by renal secretion (e.g. metformin - see below) are unlikely to be affected by VARIMAPIX.

In vitro studies demonstrate that active renal secretion of varenicline is mediated by the human organic cation transporter, OCT2. Co-administration with inhibitors of OCT2 does not require a dose adjustment of VARIMAPIX as the increase in systemic exposure to varenicline tartrate is not expected to be clinically meaningful (see cimetidine interaction below). Furthermore, since metabolism of varenicline represents less than 10 % of its clearance, medicines known to affect the cytochrome P450 system are unlikely to alter the pharmacokinetics of varenicline (see section 5.2) and therefore a dose adjustment of VARIMAPIX would not be required.

Metformin

Varenicline (1 mg twice daily) did not affect the pharmacokinetics of metformin (500 mg twice daily), which is a substrate of the organic cation transporter, OCT2.

Metformin had no effect on varenicline pharmacokinetics.

Cimetidine

Co-administration of an OCT2 inhibitor, cimetidine (300 mg four times daily), with varenicline (2 mg single dose) increased the systemic exposure of varenicline by 29 % due to a reduction in varenicline renal clearance. No dosage adjustment is recommended based on concomitant cimetidine administration.

Digoxin

Varenicline (1 mg twice daily) did not alter the steady-state pharmacokinetics of digoxin administered as a 0,25 mg daily dose.

Warfarin

Varenicline (1 mg twice daily) did not alter the pharmacokinetics of a single 25 mg dose of (R, S)-warfarin. Prothrombin time (INR) was not affected by varenicline. Smoking cessation itself may result in changes to warfarin pharmacokinetics. However, in post-marketing data there were cases of increased INR. INR should be monitored more frequently, and the warfarin dose adjusted while using VARIMAPIX, and after discontinuation of VARIMAPIX (see section 4.4).

Alcohol

There are limited clinical data on any potential interaction between alcohol and varenicline. There have been post-marketing reports of increased intoxicating effects of alcohol in patients treated with varenicline. A causal relationship between these events and varenicline use has not been established.

Some cases described unusual and sometimes aggressive behaviour and were often accompanied by amnesia for the events. Advise patients to reduce the amount of alcohol they consume while taking VARIMAPIX until they know whether VARIMAPIX affects their tolerance for alcohol.

Use with other therapies for smoking cessation

Bupropion

Varenicline (1 mg twice daily) did not alter the steady-state pharmacokinetics of

bupropion (150 mg twice daily). However, the incidence of nausea was doubled with co-administration.

Nicotine replacement therapy (NRT)

When varenicline (1 mg twice daily) and NRT (transdermal 21 mg/day) were co-administered to smokers for 12 days, there was a statistically significant decrease in average systolic blood pressure (mean 2,6 mmHg) measured on the final day of the study. In this study, the incidence of nausea, headache, vomiting, dizziness, dyspepsia, and fatigue was greater for the combination than for NRT alone.

Safety and efficacy of VARIMAPIX in combination with other smoking cessation therapies have not been studied.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Where therapy is initiated, treatment should be timed such that the course is completed before conception occurs.

Pregnancy

The safety of VARIMAPIX in human pregnancy has not been established. The use of VARIMAPIX in pregnant women is not recommended.

Breastfeeding

The safety of VARIMAPIX during lactation has not been established. Mothers on VARIMAPIX should therefore not breastfeed their infants.

Fertility

There are no clinical data on the effects of varenicline on fertility.

4.7 Effects on ability to drive and use machines

VARIMAPIX may cause dizziness, somnolence and transient loss of consciousness, and therefore may influence the ability to drive and use machines. Patients are advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether VARIMAPIX affects their ability to perform these activities.

4.8 Undesirable effects

a. Summary of the safety profile

Smoking cessation with or without treatment is associated with various symptoms. For example, dysphoric or depressed mood, insomnia, irritability, frustration or anger, anxiety, difficulty concentrating, restlessness, decreased heart rate, increased appetite or weight gain have been reported in patients attempting to stop smoking.

No attempt has been made in either the design or the analysis of the varenicline studies to distinguish between adverse events associated with study medicine treatment or those possibly associated with nicotine withdrawal.

In patients treated with the recommended dose of 1 mg twice daily following an initial titration period the adverse event most frequently reported was nausea. In the majority of cases nausea occurred early in the treatment period, was mild to moderate in severity.

b. Tabulated summary of adverse reactions

In the table below all adverse reactions, which occurred at an incidence greater than placebo are listed by system organ class and frequency: frequent, less frequent and frequency unknown.

The adverse reactions may also be associated with the underlying disease and/or concomitant medications.

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infections and infestations	Frequent	Bronchitis, nasopharyngitis, sinusitis
	Less frequent	Fungal infection, viral infection
Blood and lymphatic system disorders	Less frequent	Decreased platelet count
Immune system disorders	Frequency unknown	Hypersensitivity reactions, including angioedema
Metabolism and nutrition disorders	Frequent	Increased weight, decreased appetite, increased appetite
	Less frequent	Anorexia, diabetes mellitus , polydipsia
Psychiatric disorders	Frequent	Abnormal dreams, insomnia
	Less frequent	Feeling abnormal, crying , panic reaction, bradyphrenia, thinking abnormal, mood swings, increased libido, decreased libido, depression, mania, psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide
Nervous system disorders	Frequent	Headache, somnolence,

MedDRA system organ class	**Frequency**	**Adverse reactions**
		dizziness, dysgeusia
	Less frequent	Restlessness, cerebrovascular accident, seizure, circadian rhythm sleep disorder, tremor, coordination abnormal, dysarthria, hypertonia, dysphoria, hypoaesthesia, hypogeusia, lethargy,
	Frequency unknown	Transient loss of consciousness
Eye disorders	Less frequent	Conjunctivitis, eye pain, scotoma, scleral discolouration, eye pain, mydriasis, photophobia, myopia, lacrimation increased
Ear and labyrinth disorders	Less frequent	Tinnitus
Cardiac disorders	Less frequent	Myocardial infarction, angina pectoris, tachycardia, increased heart rate, electrocardiogram ST segment depression, decreased electrocardiogram T wave amplitude, atrial fibrillation, palpitations
Vascular disorders	Less frequent	Hot flush, increased blood pressure

MedDRA system organ class	**Frequency**	**Adverse reactions**
Respiratory, thoracic and mediastinal disorders	Frequent	Dyspnoea, cough
	Less frequent	Hoarseness, postnasal drip, upper respiratory tract inflammation, upper-airway cough syndrome, pharyngolaryngeal pain, throat irritation, respiratory tract congestion, sinus congestion, rhinorrhoea, snoring
Gastrointestinal disorders	Frequent	Toothache, nausea, gastroesophageal reflux disease, vomiting, constipation, diarrhoea, abdominal distension, abdominal pain, dyspepsia, flatulence, dry mouth
	Less frequent	Haematemesis, haematochezia, gastritis, change of bowel habit, abnormal faeces, eructation, aphthous stomatitis, gingival pain, tongue coated
Skin and subcutaneous tissue disorders	Frequent	Rash, pruritus
	Less frequent	Erythema, acne, hyperhidrosis, night sweats, serious skin reactions, including Stevens Johnson Syndrome and Erythema Multiforme, angioedema

MedDRA system organ class	**Frequency**	**Adverse reactions**
Musculoskeletal and connective tissue disorders	Frequent	Arthralgia, myalgia, back pain
	Less frequent	Joint stiffness, muscle spasms, chest wall pain, costochondritis
Renal and urinary disorders	Less frequent	Pollakiuria, glycosuria, nocturia, polyuria
Reproductive system and breast disorders	Less frequent	Menorrhagia, vaginal discharge, sexual dysfunction
General disorders and administration site conditions	Frequent	Chest pain, fatigue
	Less frequent	Chest discomfort, pyrexia, feeling cold, asthenia, malaise, cyst
Investigations	Frequent	Liver function test abnormal
	Less frequent	Semen analysis abnormal, increased C-reactive protein, decreased blood calcium

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

No cases of overdose were reported in pre-marketing clinical trials.

In case of overdose, standard supportive measures should be instituted as required. Varenicline has been shown to be dialyzed in patients with end stage renal disease (see section 5.2), however, there is no experience in dialysis following overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification: A 34 Other

Pharmacotherapeutic group: Other nervous system drugs; Drugs used in addictive disorders; Drugs used in nicotine dependence, ATC code: N07BA03

Varenicline binds at the α4β2 neuronal nicotinic acetylcholine receptors, where it acts as a partial agonist - a compound that has both agonist and antagonist activities, with lower intrinsic efficacy than nicotine, and antagonist activities in the presence of nicotine.

Electrophysiology studies *in vitro* and neurochemical studies *in vivo* have shown that varenicline binds to the α4β2 neuronal nicotinic acetylcholine receptors and stimulates receptor-mediated activity, but at a significantly lower level than nicotine.

Nicotine competes for the same human α4β2 nAChR binding site for which varenicline has higher affinity. Therefore, varenicline can effectively block the ability of nicotine to activate the α4β2 receptor and the mesolimbic dopamine system, the neuronal mechanism underlying reinforcement and reward experienced upon smoking.

Varenicline is highly selective and binds more potently to the α4β2 receptor subtype than to other common nicotinic receptors (> 500-fold α3β2, > 3 500-fold α47, > 20 000-fold α1βγδ), or to non-nicotinic receptors and transporters (> 2 000-fold).

5.2 Pharmacokinetic properties

Absorption

Maximum plasma concentrations of varenicline tartrate occur typically within 3 - 4 hours after oral administration. Following administration of multiple oral doses to healthy volunteers, steady-state conditions were reached within 4 days.

Absorption is virtually complete after oral administration and systemic availability is high. Oral bioavailability of varenicline tartrate is unaffected by food or time-of-day dosing.

Distribution

Varenicline distributes into tissues, including the brain. Apparent volume of distribution averaged 415 L (% CV= 50) at steady state.

Plasma protein binding of varenicline tartrate is low (≤ 20 %) and independent of both age and renal function.

Biotransformation

Varenicline tartrate undergoes minimal metabolism with 92 % excreted unchanged in the urine and less than 10 % as metabolites. Minor metabolites in urine include varenicline N-carbamoylglucuronide and hydroxyvarenicline. In circulation, varenicline comprises 91 % of medicine-related material. Minor circulating metabolites include varenicline N-carbamoylglucuronide and N glucosylvarenicline.

Elimination

The elimination half-life of varenicline tartrate is approximately 24 hours. Renal elimination of varenicline tartrate is primarily through glomerular filtration along with active tubular secretion via the organic cationic transporter, OCT2 (see section 4.5).

Pharmacokinetics in special patient populations

There are no clinically meaningful differences in varenicline tartrate

pharmacokinetics due to age, race, gender; smoking status as demonstrated in specific pharmacokinetic studies and in population pharmacokinetic analyses.

Renal insufficiency

Varenicline tartrate pharmacokinetics were unchanged in subjects with mild renal impairment (estimated creatinine clearance > 50 ml/min and ≤ 80 ml/min). In patients with moderate renal impairment (estimated creatinine clearance ≥ 30 ml/min and ≤ 50 ml/min), varenicline tartrate exposure increased 1,5-fold compared with subjects with normal renal function (estimated creatinine clearance > 80 ml/min). In subjects with severe renal impairment (estimated creatinine clearance < 30 ml/min), varenicline tartrate exposure was increased 2,1 -fold. In subjects with end-stage-renal disease (ESRD), varenicline tartrate was removed by haemodialysis. No dosing adjustment is necessary for patients with mild to moderate renal impairment and a reduced dosing frequency of 1 mg once daily is recommended for patients with severe renal impairment (see section 4.2). Dosing should begin at 0,5 mg once daily for the first 3 days, and then increased to 1 mg once daily.

Elderly

No dosage adjustment is necessary for elderly patients (see section 4.2). A combined single and multiple-dose pharmacokinetic study demonstrated that the pharmacokinetics of 1 mg varenicline tartrate given once or twice daily to 16 healthy elderly male and female smokers (aged 65 - 75 years) for 7 consecutive days was similar to that of younger subjects.

Paediatric population

Because the safety and effectiveness of varenicline in paediatric patients have not been established, varenicline is not recommended for use in patients under 18 years of age.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core (0,5 mg and 1 mg tablets):

Anhydrous dibasic calcium phosphate

Colloidal silicon dioxide

Croscarmellose sodium

Magnesium stearate

Microcrystalline cellulose

Film coating (0,5 mg tablet):

Hypromellose 2910

Polyethylene glycol 400

Titanium dioxide (E171)

Film coating (1 mg tablet):

FD&C Blue No. 2--aluminium lake

Hypromellose 2910

Polyethylene glycol 400

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 30 °C.

Keep the blisters in the carton until required for use.

6.5 Nature and contents of container

Starter (initial dosing) pack containing 2 PVC hard film blisters: one blister of 11 x VARIMAPIX 0,5 mg film-coated tablets and one blister of 14 x VARIMAPIX 1 mg film-coated tablets. Blisters are packed in a secondary card packaging, and heat-sealed with aluminium foil bags, then packed in a carton with leaflet.

Starter (initial dosing) pack containing 4 PVC hard film blisters: one blister of 11 x VARIMAPIX 0,5 mg film-coated tablets and three blisters of 14 x VARIMAPIX 1 mg film-coated tablets. Blisters are packed in a secondary card packaging, and heat-sealed with aluminium foil bags, then packed in a carton with leaflet.

Follow-on (maintenance) pack containing 2 or 4 PVC hard film blisters of 14 x VARIMAPIX 1 mg film-coated tablets. Blisters are packed in a secondary card packaging, and heat-sealed with aluminium foil bags, then packed in a carton with leaflet.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBERS

VARIMAPIX 0,5 mg: 56/34/0115

VARIMAPIX 1 mg: 56/34/0116

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18 June 2024

10 DATE OF REVISION OF THE TEXT

21 May 2026