PROFESSIONAL INFORMATION

SCHEDULING STATUS S5

1 NAME OF THE MEDICINE

NIKABEX® 0,5; 0,5 mg film-coated tablets

NIKABEX® 1; 1 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

Sugar free.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.

NIKABEX 0,5: White to off-white, capsular shaped, biconvex film-coated tablets debossed with “C2” on one side and plain on other side.

NIKABEX 1,0: Light blue, capsular shaped, biconvex film-coated tablets debossed with “C1” on one side and plain on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

NIKABEX is indicated as an aid to smoking cessation in patients committed to stop smoking, in addition to a behaviour modification programme, for 12 weeks. Efficacy beyond 12 weeks has not been determined.

4.2 Posology and method of administration

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.

Posology

Patients should be treated with NIKABEX for 12 weeks.

The recommended dose is 1 mg NIKABEX 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 to end of treatment:	1 mg twice daily

The patient should set a date to stop smoking. NIKABEX dosing should usually start at 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. Dose tapering of NIKABEX is not required at the end of treatment.

Special populations

Renal impairment

No dosage adjustment is necessary for patients with mild to moderate renal impairment.

For patients with severe renal impairment, the recommended dose of NIKABEX 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).

Hepatic impairment

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

Elderly

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

NIKABEX is not recommended for use in patients under 18 years of age because safety and efficacy in this population have not been established (see section 5.2).

Method of administration

NIKABEX is for oral use and the tablets should be swallowed whole with water. NIKABEX can be taken with or without food.

4.3 Contraindications

Hypersensitivity to varenicline or to any of the excipients of NIKABEX, listed in 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 NIKABEX, may alter the pharmacokinetics or pharmacodynamic properties of some medicines, for which dosage adjustment may be necessary (examples include theophylline, warfarin and insulin). Cases of increased international normalised ratio (INR) have been reported. INR should be monitored more frequently and the warfarin dose adjusted while taking NIKABEX, and after discontinuation of NIKABEX (see section 4.5).

As smoking induces CYP1A2, smoking cessation may result in an increase of plasma levels of CYP1A2 substrates.

Neuropsychiatric symptoms

Serious neuropsychiatric symptoms have been reported in patients being treated with varenicline (as in NIKABEX).

Changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, hostility, agitation, anxiety, panic, mood swings, aggressive behaviour, suicidal ideation and behaviour and suicide attempts (including completed suicide – see section 4.8) have been reported in patients attempting to quit smoking with NIKABEX in the post-marketing experience.

Depressed mood, rarely including suicidal ideation and suicide attempt, may be a symptom of nicotine withdrawal.

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, rarely including suicidal ideation, has been reported in smokers trying to stop smoking without medicinal treatment. However, some of these symptoms have occurred in patients taking varenicline (as in NIKABEX) who continued to smoke. When symptoms were reported, most were during varenicline treatments, but some were following discontinuation of varenicline (as in NIKABEX) treatment. These events have occurred in patients with and without pre-existing psychiatric disease; some patients have experienced worsening of their psychiatric illnesses.

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 while on NIKABEX treatment, patients should discontinue NIKABEX immediately and contact a healthcare professional for re-evaluation of treatment.

In many post-marketing cases, resolution of symptoms after discontinuation of varenicline (as in NIKABEX) was reported, although in some cases the symptoms persisted, therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

History of psychiatric disorders

Smoking cessation, with or without pharmacotherapy, has been associated with exacerbation of underlying psychiatric illness (e.g. depression).

Neuropsychiatric adverse events were reported more frequently in patients with a history of psychiatric disorders compared to those without a history of psychiatric disorders, regardless of treatment (see section 5.1).

Care should be taken with patients with a history of psychiatric illness and patients should be advised accordingly.

Seizures

There have been reports of seizures in patients with or without a history of seizures, treated with varenicline, as in NIKABEX. NIKABEX 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 in NIKABEX) was associated with an increase in irritability, urge to smoke, depression, and/or insomnia in up to 3 % of patients. The prescriber should inform the patient accordingly and discuss or consider the need for dose tapering.

Cardiovascular events

After cessation of smoking, cardiovascular events were reported more frequently in patients with stable cardiovascular disease that were treated with varenicline (as in NIKABEX). Cardiovascular events occurred primarily in patients with known cardiovascular disease.

Patients taking NIKABEX should be instructed to notify their medical practitioner of new or worsening cardiovascular symptoms and to seek immediate medical attention if they experience signs and symptoms of myocardial infarction or stroke (see section 5.1).

Angioedema and hypersensitivity reactions

There have been post-marketing reports of hypersensitivity reactions including angioedema in patients treated with varenicline (as in NIKABEX). Clinical signs included swelling of the face, mouth (tongue, lips, and gums), neck (throat and larynx) and extremities. There were infrequent reports of life-threatening angioedema requiring urgent medical attention due to respiratory compromise. Patients experiencing these symptoms

should discontinue treatment with NIKABEX and contact a healthcare provider immediately.

Serious skin reactions

There have also been post-marketing reports of serious skin reactions, including Stevens-Johnson syndrome and erythema multiforme in patients taking varenicline (as in NIKABEX); see section 4.8. As these skin reactions can be life-threatening, patients should discontinue treatment at the first sign of a skin rash or skin reaction and contact a healthcare provider immediately.

4.5 Interaction with other medicines and other forms of interaction

Based on varenicline characteristics and clinical experience to date, NIKABEX has no clinically meaningful medicine interactions. No dosage adjustment of NIKABEX or co-administered medicines listed below is recommended.

In vitro studies indicate that varenicline is unlikely to alter the pharmacokinetics of compounds that are primarily metabolised by cytochrome P450 enzymes.

Furthermore, since metabolism of varenicline represents less than 10 % of its clearance, active substances 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 NIKABEX would not be required.

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

Metformin

Varenicline did not affect the pharmacokinetics of metformin. Metformin had no effect on varenicline pharmacokinetics.

Cimetidine

Co-administration of cimetidine, with varenicline 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 in patients with normal renal function or in patients with mild to moderate renal impairment. In patients with severe renal impairment, the concomitant use of cimetidine and NIKABEX should be avoided.

Digoxin

Varenicline did not alter the steady-state pharmacokinetics of digoxin.

Warfarin

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

Use with other therapies for smoking cessation

Bupropion

Varenicline did not alter the steady-state pharmacokinetics of bupropion.

However, the incidence of nausea is doubled with co-administration.

Nicotine replacement therapy (NRT)

When varenicline and transdermal NRT 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 NIKABEX in combination with other smoking cessation therapies have not been studied.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential

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

Pregnancy

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

Lactation

The safety of NIKABEX during lactation has not been established. Mothers on NIKABEX 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

NIKABEX may have minor or moderate influence on the ability to drive and use machines. However, NIKABEX 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 this medicine 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. No attempt has been made in either the design or the analysis of the NIKABEX studies to distinguish between adverse reactions 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 (28,6 %). In the majority of cases nausea occurred early in the treatment period, and was mild to moderate in severity.

b. Tabulated summary of adverse reactions

System organ class	**Adverse reactions**
Infections and infestations	
Frequent	Nasopharyngitis, bronchitis, sinusitis
Less frequent	Fungal infection, viral infection
Immune system disorders	
Not known	Hypersensitivity reactions, angioedema
Blood and lymphatic system disorders	
Less frequent	Platelet count decreased
Metabolism and nutrition disorders	
Frequent	Weight increased, increased appetite, decreased appetite
Less frequent	Hyperglycaemia, diabetes mellitus, polydipsia

Psychiatric disorders

Frequent	Abnormal dreams, insomnia
Less frequent	Suicidal ideation, aggression, panic reaction, thinking abnormal, restlessness, mood swings, depression*, anxiety*, hallucinations*, libido increased, libido decreased, psychosis, somnambulism, abnormal behaviour, dysphoria, bradyphrenia

Nervous system disorders

Frequent	Headache, somnolence, dizziness, dysgeusia
Less frequent	Seizure, tremor, lethargy, hypoaesthesia, cerebrovascular accident, hypertonia, dysarthria, coordination abnormal, hypogeusia, circadian rhythm sleep disorder
Not known	Transient loss of consciousness

Eye disorders

Less frequent	Conjunctivitis, eye pain, scotoma, scleral discolouration, mydriasis, photophobia, myopia, lacrimation increased

Ear and labyrinth disorders

Less frequent	Tinnitus

Cardiac disorders

Less frequent	Myocardial infarction, angina pectoris, tachycardia, palpitations, heart rate increased, atrial fibrillation, electrocardiogram ST segment depression, electrocardiogram T wave amplitude decreased

Vascular disorders

Less frequent	Blood pressure increased, hot flush

Respiratory, thoracic and mediastinal disorders

Frequent	Dyspnoea, cough

Less frequent	Upper respiratory tract inflammation, respiratory tract congestion, dysphonia, rhinitis allergic, throat irritation, sinus congestion, upper- airway cough syndrome, rhinorrhoea, laryngeal pain, snoring

Gastrointestinal disorders

Frequent	Nausea, gastroesophageal reflux disease, vomiting, constipation, diarrhoea, abdominal distension, abdominal pain, toothache, dyspepsia, flatulence, dry mouth
Less frequent	Haematochezia, gastritis, change of bowel habit, eructation, aphthous stomatitis, gingival pain, haematemesis, abnormal faeces, tongue coated

Skin and subcutaneous tissue disorders

Frequent	Rash, pruritus
Less frequent	Erythema, acne, hyperhidrosis, night sweats, severe cutaneous reactions, including Stevens-Johnson syndrome and erythema multiforme

Musculoskeletal and connective tissue disorders

Frequent	Arthralgia, myalgia, back pain
Less frequent	Muscle spasms, musculoskeletal chest pain, joint stiffness, costochondritis

Renal and urinary disorders

Less frequent	Pollakiuria, nocturia, glycosuria, 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, influenza like illness, pyrexia, asthenia, malaise, feeling cold, cyst

Investigations

Frequent	Liver function test abnormal
Less frequent	Semen analysis abnormal, C-reactive protein increased, blood calcium decreased.

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. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

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 dialysed 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

Category and class: A 2.11 Other medicines acting on the central nervous system

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

Mechanism of action

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.

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 lower level than nicotine. Varenicline blocks nicotine's ability to activate α4β2 receptors. Varenicline is highly selective and binds more potently to the α4β2 receptor subtype than to other common nicotinic receptors (> 500-fold α3β4, > 3 500-fold α7, >20 000-fold α1βγδ), or to non-nicotinic receptors and transporters (> 2 000-fold).

5.2 Pharmacokinetic properties

Absorption

Maximum plasma concentrations of varenicline 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

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.

Elimination

The elimination half-life of varenicline 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, or use of concomitant medicines, as demonstrated in specific pharmacokinetic studies and in population pharmacokinetic analyses.

Renal impairment

Varenicline tartrate pharmacokinetics were unchanged in patients 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 patients with normal renal function (estimated creatinine clearance > 80 ml/min). In patients with severe renal impairment (estimated creatinine clearance < 30 ml/min), varenicline tartrate exposure was increased 2,1-fold. In patients with end stage renal disease (ESRD), varenicline tartrate was efficiently removed by haemodialysis (see section 4.2).

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).

Hepatic impairment

Due to the absence of significant hepatic metabolism, varenicline tartrate pharmacokinetics should be unaffected in patients with hepatic impairment (see section 4.2).

Elderly

No dosage adjustment is necessary for elderly patients (see section 4.2). The pharmacokinetics of varenicline tartrate in elderly patients with normal renal function (aged 65-75 years) is similar to that of younger adult patients. For elderly patients with reduced renal function please refer to section 4.2.

Paediatric population

NIKABEX is not recommended in paediatric patients under 18 years of age because its efficacy in this population was not demonstrated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

0,5 mg and 1 mg tablets

Croscarmellose sodium

Maltodextrin

Microcrystalline cellulose

Stearic acid

Film coating

0,5 mg tablet

Hydroxypropyl cellulose (E463)

Hypromellose (E464)

Talc

Titanium dioxide (E171)

1 mg tablet

FD&C Blue #2 / Indigo Carmine Aluminium Lake E132

Hydroxypropyl cellulose (E463)

Hypromellose (E464)

Talc

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

NIKABEX is available in blister strips of transparent PVC Armour film with silver aluminium foil lidding, packed in printed folding carton.

Pack sizes:

Starter (initial dosing) pack containing 2 blister strips: one blister strip of 11 x NIKABEX 0,5 film-coated tablets and one blister strip of 14 x NIKABEX 1 film-coated tablets.

Starter (initial dosing) pack containing 4 blister strips: one blister strip of 11 x NIKABEX 0,5 film-coated tablets and three blister strips of 14 x NIKABEX 1 film-coated tablets.

Follow-on (maintenance) pack containing two or four blister strips of 14 x NIKABEX 1 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATES OF REGISTRATION

Abex Pharmaceutica (Pty) Ltd

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0181

8 REGISTRATION NUMBERS

NIKABEX 0,5: 55/2.11/0515

NIKABEX 1: 55/2.11/0516

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 May 2023

10 DATE OF REVISION OF THE TEXT

Not applicable