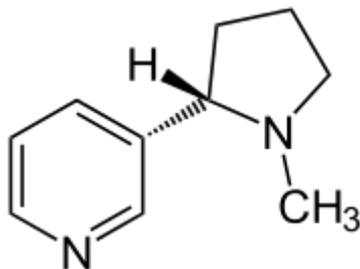


## Cytisine (Tabex®) and psychosis –an update

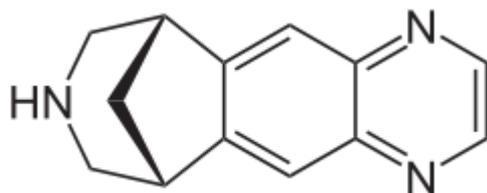
### Introduction

Tabex® has been licensed in Eastern Europe as an aid to smoking cessation for 40 years. In Netherlands, the drug Tabex® is not registered through the Dutch Medicines Evaluation Board (CBG). The drug is produced in Bulgaria and can be purchased via internet. The active substance in Tabex® is cytisine. The molecular structure of cytisine has similarity to that of varenicline [1]. Varenicline is registered in European Union in 2006 as a drug for smoking cessation therapy, admitted to the European market under the brand name Champix® and in USA under the brand name Chantix® [2]. Varenicline was discovered through the synthesis of a series of compounds inspired by the natural product cytisine, which was previously known to have partial agonist activity at the  $\alpha 4 \beta 2$  acetylcholine receptor ( $\alpha 4 \beta 2$  nAChR). Varenicline displaying ~30–60% of the in vivo efficacy of nicotine, and it also effectively blocks the in vivo response to nicotine [3].

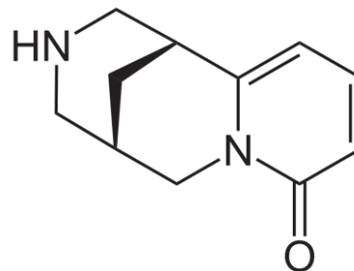
### Structural formulas



nicotine



varenicline



cytisine

In 2017 Netherland Pharmacovigilance Centre Lareb informed the Inspectorate for Healthcare and Youth (IGJ) about the 2 cases of psychosis related to the use of Tabex®. Lareb also has paid attention to this via a news item on the website [4].

Recently Lareb received a new case of this serious adverse drug reaction after using Tabex®. This overview is an update on the received cases.

### Reports

In March 2016, December 2016 and July 2019 Lareb received reports concerning patients who developed a psychosis after use of Tabex® for smoking cessation. Two reports were submitted by a psychiatrist ( caseA and B) and one report (case C) was reported by a patient.

Case A (report number 217162): A psychiatrist working at a mental health care facility reported about a 41-50 years-old female who developed a psychosis 34 days after start of Tabex® for smoking

cessation. The product Tabex® was withdrawn. The patient was treated with haloperidol. At the time of reporting, the patient was recovering. Concomitant medication was not reported. The reporter mentions that stress around the time of the event could be an alternative or additional cause for the reaction.

Case B (report number 231406): A Physician working at a mental health care facility reported about a 51-60 years-old woman who was hospitalized during 3 weeks due to a psychosis following administration of Tabex® for smoking cessation. The dosage used was 6 times daily 1.5 mg. The reaction occurred 1 week after start. Tabex® was withdrawn. The patient was treated with haloperidol 3 mg daily and was recovering at the time of the reporting. Concomitant medication was pantoprazole. The reporter mentions that stress around the time of the event could be an alternative or additional cause for the reaction. The patient has a medical history of a post-partum depression and psychosis in 2002.

Case C (report number 00342430 ): A female aged 41-50 years reported that she developed a psychosis after 3 weeks of using Tabex® for smoking cessation therapy. She also experienced palpitations and depressed mood. The recommended use implies a tapering down dosage schedule of Tabex® started with 6 tablets first few days and then in intervals decreasing by 1 tablet. The symptoms started at the dosage of 2 tablets per day, this is according to the schedule after 21 days of therapy. The patient also used paroxetine, already for 20 years. The symptoms were treated with (non specified) "calming" and antiarrhythmic medication, prescribed by her general practitioner. The patient was recovering at the time of notification but she describes this period as something terrible to experience.

### **Product information Tabex® [5]**

The patient's leaflet recommends to use 1st to 3rd day 1 tablet every 2 hours (6 tablets per day) with a contemporary reduction in the number of smoked cigarettes and stop smoking not later than the fifth day. From day 3 a tapering down regime is recommended ending at day 21 with 2-3 tablets per day.

According to the product information, clinical studies for this product showed good tolerance to the drug and serious side effects were not observed. The following side effects are summarized: changes in both taste and appetite, dryness in the mouth, headache, irritability, nausea, constipation, increased heartbeat, slight increase in blood pressure. No data is available from unwanted interactions between Tabex® and other medicines. Symptoms of nicotine poisoning observed in Tabex® overdose are nausea, vomiting, dilated pupils, faster than normal heartbeat, general weakness, clonic convulsions, paralysis of breathing.

### **Other sources of information**

#### *Literature*

The studies on cytisine as a smoking cessation drug, found in the literature revealed no serious adverse events. The most frequently reported adverse reactions were gastrointestinal complaints such as dry mouth, stomachache, nausea and gastric disturbances [6,7,8,9].

The National Institute for Public Health and Environment (RIVM) placed in the 'Evaluation of the Health risks associated with so-called banned herbs' another cytisine containing herb *Genista tinctoria* (dyer's greenweed) on the list of the banned herbs. Herbs Laburnum and Cytisus, the source of cytisine in Tabex®, are not listed in this report [10].

#### *Mechanism*

Cytisine is an alkaloid that occurs naturally in several plant genera, such as Laburnum and Cytisus (Golden Rain, acacia) of the family Fabaceae. Like varenicline, cytisine is a partial agonist of nicotinic acetylcholine receptors. Cytisine binds with high affinity to the  $\alpha_3\beta_2$  subtype of the nicotinic acetylcholine receptor [11,12]. This receptor subtype has been implicated in the development and maintenance of nicotine dependence [13] and was the primary target for the drug varenicline, which has proved effective in aiding smoking cessation [14]. In vitro and in vivo results suggest that in nicotine addiction, cytisine would moderately increase the dopamine level in the mesolimbic system,

attenuating the withdrawal symptoms. On the other hand, it should minimize the addictive effects of nicotine by decreasing the dopamine level [11,12]. Studies in varenicline have shown that the risk of developing psychotic symptoms is greater for people with previous mental illness. Secondary psychotic episodes seem to be a possible side effect of treatment with this drug. However, one case report describes an acute psychotic reaction in a patient with no previous psychiatric history including alcohol or illicit drug abuse and no known psychiatric family history [15]. Studies in nonhuman species have shown that cytisine does not cross the blood–brain barrier well, and it has been argued that, at the dose used for smoking cessation, cytisine would be expected to have limited efficacy [16]. But it is not clear whether the data from nonhuman species can be generalized to humans, and the findings noted above indicate the need for a full-scale efficacy trial that conforms to modern standards [6].

## Discussion and conclusion

Cytisine (Tabex<sup>®</sup>) is used to help with smoking cessation [1]. Its molecular structure has some similarity to that of varenicline (Champix<sup>®</sup>) and it has similar pharmacological effects. Whereas varenicline is a licensed product in Netherlands, cytisine (Tabex<sup>®</sup>) is not. Tabex<sup>®</sup> can be ordered by the Dutch consumers illegal via internet. Economical, due to the price difference between Champix<sup>®</sup> and Tabex<sup>®</sup> many consumers choose for the cheaper product Tabex<sup>®</sup>. Champix<sup>®</sup> is a prescription product but not included in the drug reimbursement system. The consumers using it are under the supervision of their prescriber, the users of Tabex<sup>®</sup> are not. Psychiatric adverse reactions are well known en mentioned in the Summary of the Product Characteristics (SmpC) and in the patient leaflet (PIL) of the Champix<sup>®</sup>. But no psychiatric and/ or severe adverse reactions are mentioned in the original Sopharma product information of Tabex<sup>®</sup>. Only drowsiness, sleeplessness and increase in irritability are summarized. Under the contraindication mental disease (some form of schizophrenia) has been mentioned. Since Tabex<sup>®</sup> has no marketing authorization in the Netherlands no official Dutch PIL is available. But the Dutch website ikstop.nl, where Tabex<sup>®</sup> is recommended as one of the possible treatments in smoking cessation, provides an automatic translation (powered by Google) of the PIL from the Sopharma. However, this is incomplete translation and does not mention all the side effects named in the manufacturer's original English PIL. The information on contraindications, including mental disease is missing here. It is only mentioned that Tabex<sup>®</sup> is contraindicated in arterial hypertension and advanced atherosclerosis. The consumers who purchase Tabex<sup>®</sup>, and don't understand English, only read the Dutch patient information on the website. Unfortunately this information is incomplete and therefore may be misleading.

Based on the reported 3 cases of psychosis, and the similarity with varenicline, it is a potential safety-risk that this product is available on the Dutch market. The risk is probably even bigger due to the lack of complete Dutch safety information.

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*This signal has been raised on August 23, 2019. It is possible that in the meantime other information became available.*