1.1. Cytisine (Tabex®) and psychosis

Introduction
Tabex® has been licensed in Eastern Europe as an aid to smoking cessation for 40 years. In the Netherlands, the drug Tabex® is not registered. The drug is produced in Bulgaria and can be illegal purchased via internet. The active substance in Tabex® is cytisine. The molecular structure of cytisine has similarity to that of varenicline [1]. Varenicline was registered in the European Union in 2006 as a drug for smoking cessation therapy, under the brand name Champix®. It is available in the 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 α4β2 acetylcholine receptor (α4β2 nAChR). Varenicline displays ~30–60% of the in vivo efficacy of nicotine, and it also effectively blocked the in vivo response to nicotine [3].

Structural formulas

nicotine

varenicline
cytisine

Reports
In March 2016 and December 2016 Lareb received 2 reports concerning patients who developed psychosis after use of Tabex® for smoking cessation.

Case A (report number 217162): A Psychiatrist working at a mental health care facility reported about a female 41–50 years 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 The product Tabex® was withdrawn.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 women 51–60 years who was hospitalized during 3 weeks due to the 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 Tabex® was withdrawn.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.
Other sources of information

**Literature**

On the website promoting Tabex®, the following information on adverse reaction is given: “the clinical studies showed a good tolerance to the drug and grave adverse effects were not observed. The following adverse effects are rather often observed at the beginning of Tabex® treatment: changes in both taste and appetite, dryness in the mouth, headache, irritability, nausea, constipation, tachycardia, light elevation of the arterial pressure. The majority of the adverse effects can abate in the course of the treatment” [4].

The studies on cytisine as a smoking cessation drug, found in the literature [5,6,7,8] revealed no serious adverse events. The most frequently reported adverse reactions were gastrointestinal complaints such as dry mouth, stomatchache, nausea and gastric disturbances. No serious adverse effects were reported in the trials, however Zatonski W et al. [8] mention the documentation and design of these studies would not be considered sufficient to support registration in European countries because of, among other things, lack of longer-term follow-up, clear definitions of sustained abstinence, and absence of biochemical verification.

The National Institute for Public Health and Environment (RIVM) have reported on the Evaluation of the Health risks associated with so-called banned herbs. The list of banned herbs mentions another cytisine containing herb Genista tinctoria (dyer’s greenweed). The herbs Laburnum and Cytisus, the source of cytisine in Tabex®, are not listed in this report [9].

**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 α6β, subtype of the nicotinic acetylcholine receptor [10,11]. This receptor subtype has been implicated in the development and maintenance of nicotine dependence [12] and was the primary target for the drug varenicline, which has proved effective in aiding smoking cessation [13]. 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, and on the other hand, it should minimize the addictive effects of nicotine by decreasing the dopamine level [10,11]. 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 in literature a case report of an acute psychotic reaction in a patient with no previous psychiatric history including alcohol or illicit drug abuse and no known psychiatric family history, has been described [14].

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 [15]. 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 [5].

**Discussion and conclusion**

Cytisine (Tabex®) is used to help with smoking cessation [1]. Its molecular structure has some similarity to that of varenicline (Champix®) and it has similar pharmacological effects. Whereas varenicline is a licensed product, cytisine (Tabex®) is not. Champix is a prescription product but not included in the drug reimbursement system, although it is (partially) reimbursed by some Healthcare Insurance Companies. Tabex® can be ordered by Dutch consumers via internet. Due to the price difference between Champix® and Tabex® many consumers choose for the cheaper product Tabex®. The consumers using it are under the supervision of their prescriber, the users of Tabex® are not. Psychiatric adverse reactions are well known en mentioned in the Summary of the Product Characteristic (SmpC) and in the patient leaflet (PIL) of the Champix®. But no psychiatric and/ or severe adverse reactions are mentioned in the product information of Tabex®. Only some gastrointestinal adverse reactions are summarized. The consumer information contains no warning for the history of the psychiatric episodes. Since this product has no marketing authorization in the Netherlands, and is thus illegal on the market, and based on the similarity between the chemical
structure and the pharmacologic effectiveness with varenicline and the reported two cases of psychosis, it is a potential safety-risk that this product is available on the Dutch market.

References

14. Forcen FE, Martinez FLE, Moya AM, Varenicline Precipitating Psychosis in a Patient with no Previous Psychiatric History: A Case Report of a Spanish Patient Who was Later Diagnosed with Paranoid Personality Disorder, Clinical Schizophrenia & Related Psychoses October 2011

This overview was published on June 19, 2017. It is possible that in the meantime other information became available.