

Memorandum

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Date: **OCT 6 2006**

From: Consumer Safety Officer, Division of Dietary Supplement Programs, Office of Nutritional Products, Labeling and Dietary Supplements, HFS-810

Subject: 75-Day Premarket Notification of New Dietary Ingredients

To: Dockets Management Branch, HFA-305

Subject of the Notification: *Cytisus labroinu* [sic]

Firm: National Center for Tobacco Research

Date Received by FDA: June 28, 2006

90-Day Date: September 29, 2006

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification and related correspondence for the aforementioned substance should be placed on public display in docket number 95S-0316 as soon possible since it is past the 90-day date. Thank you for your assistance.

____Victoria Lutwak____

1995S-0316

RPT 357



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

5100 Paint Branch Parkway
Food and Drug Administration
College Park, Maryland 20740

SEP - 7 2006

Kirk G. Voelker, M.D.
National Center for Tobacco Research
1537 State Street
Sarasota, Florida 34236

Dear Dr. Voelker:

This is to inform you that the notification, dated June 21, 2006, you submitted pursuant to 21 U.S.C. 350b(a)(2)(section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)) was filed by the Food and Drug Administration (FDA) on June 28, 2006. Your notification concerns the substances called "cytisine," extracted from the plant "*Cytisus labroinu [sic]*," that you intend to market as a new dietary ingredient.

According to your notification the extract, "cytosine," will be in a tablet form. The suggested or recommended conditions of use for "cytosine" are the following: "The usual dosage of cytosine[sic] is 1.5mg table four times a day."

Under 21 U.S.C. 350b(a), the manufacturer or distributor of a dietary supplement containing a new dietary ingredient that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered must submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under section 350b (a) (2), there must be a history of use or other evidence of safety establishing that the new dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is considered to be adulterated under 21 U.S.C. 342(f) (1) (B) because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury.

Your notification does not comply with the requirements of 21 CFR 190.6 and is incomplete. Your submission did not include an original and two copies of the notification. Your notification did not provide a description of the dietary supplement that contains the new dietary ingredient. You did not provide a history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. In addition, FDA requires full citations to published articles which are the basis on which you conclude that your product will reasonably be expected to be safe. Any references to published information offered in support of the notification shall be accompanied by reprints or photostatic copies of such references. If any part of the material submitted is in a foreign language, it shall be accompanied by an accurate and complete English translation.

FDA is unable to determine whether the scientific study cited in your notice provides an adequate basis for a conclusion that the dietary supplement will reasonably be expected to be safe because the information contained in your notice is incomplete. If you market your product without submitting a notification that meets the requirements of 21 CFR 190.6 or market your product less than 75 days after submitting such a notification, your product is considered adulterated under 21 U.S.C. 342(f)(1)(B) as a dietary supplement that contains a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury. Introduction of such a product into interstate commerce is prohibited under 21 U.S.C. 331(a) and (v).

Your notification will be kept confidential for 90 days after the filing date of June 28, 2006. After the 90-day date, the notification will be placed on public display at FDA's Docket Management Branch in docket number 95S-0316. Prior to that date, you may wish to identify in writing specifically what information you believe is proprietary, trade secret or otherwise confidential for FDA's consideration.

If you have any questions concerning this matter, please contact Victoria Lutwak at (301) 436-1775.

Sincerely yours,

A handwritten signature in cursive script that reads "Linda S. Pellicore".

Linda S. Pellicore, Ph.D.
Supervisory Team Leader, Senior Toxicologist
Division of Dietary Supplement Programs
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety and Applied Nutrition

National Center for Tobacco Research

Division of Standards and Labeling Regulations
Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-820)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD, 20740-3835

June 21, 2006

Food and Drug Administration,

Pursuant to section 412 of Act 21 U.S.C. 305b, we are applying for premarket registration of a new dietary ingredient. The ingredient is a natural herbal extract, cytosine, extracted from the plant *Cytisus labroinu* L., also called "Golden Rain", widespread in the southern areas of Central Europe and Italy. All parts of the plant contain the alkaloid cytosine, the greatest amount (up to 3%) being found in the seeds. The extract is unadulterated and not chemically altered or otherwise manipulated.

Currently the main supplier of natural cytosine tablets is a Bulgarian company Sopharma. Their cytosine product is called Tabex. Each Tabex capsule contains 1.5mg of cytosine. Cytosine has been safely used for over 40 years in Eastern Europe for various indications including smoking cessation. Recently, cytosine has been **shown to increase dopamine release in the brain in a manner similar to nicotine ($\alpha 4\beta 2$ subunits of the nicotine receptors)**. The usual dosage of cytosine is 1.5mg tablet four times a day.

In a recent study (enclosed) of 436 patients who used natural cytosine to help quit smoking, there were only minor side effects of dryness of mouth, nausea and gastric disturbance in around 10-15%.

Our plans are to import limited quantities in order to research and evaluate this herbal product as a natural adjunct in smoking cessation.

Please feel free to contact me directly if you have any questions. My toll free number is 877 576-1434.

Sincerely,


Kirk G. Voelker, M.D.

National Center for Tobacco Research
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An uncontrolled trial of cytisine (Tabex) for smoking cessation

Witold Zatonski¹, Magda Cedzynska¹, Piotr Tutka², Robert West³

Abstract

Objectives: Cytisine (Tabex) has been licensed in Eastern Europe as an aid to smoking cessation for 40 years. Cytisine is a partial agonist with high affinity binding to the alpha-4, beta-2 nicotinic acetylcholine receptor believed to be central to the rewarding effect of nicotine. There is insufficient information on effectiveness to warrant licensing by modern standards. To assess whether full-scale controlled trials are warranted we sought to obtain an estimate of the 12-month continuous abstinence rates of smokers using Tabex (cytisine) with minimal behavioural support.

Design: An uncontrolled, open-label trial.

Setting: A smokers' clinic in an oncology centre in Warsaw, Poland.

Subjects: 436 consecutive attendees of the smokers' clinic of whom 191 were male. The mean dependence score (Fagerstrom Test for Nicotine Dependence) was 6.1.

Intervention: The standard regimen of Tabex was used, involving 25 days of treatment with minimal behavioural support.

Main outcome measure: Self-reported continuous abstinence for 12 months; with abstinence verified by CO at the final follow up (after 12 months).

Results: 60 participants (13.8% of the total sample) were abstinent for 12 months. Of the 315 subjects, who had taken the drug, 49 (15.5%) stopped cytisine due to adverse effects (mostly gastric disturbances and nausea), although they were not serious. The frequency of the minor adverse effects, primarily gastric disturbance was similar to that observed in previous studies with the drug.

Conclusions: The long-term abstinence rates were similar to those observed in smokers receiving nicotine replacement therapy. Full-scale randomised trials of cytisine, conducted to the standards required by regulatory authorities, are warranted.

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What is known: Cytisine, medication licensed in Eastern Europe for 40 years as an aid to smoking cessation, appears to improve abstinence rates in smokers attempting to stop but existing studies have not included long-term follow-up or have adopted inadequate abstinence criteria.

What this study adds: The 12-month carbon-monoxide verified continuous abstinence rate following a standard course of treatment with cytisine with minimal behavioural support was found in 436 smokers to be similar (13.8%) to that observed following treatment with nicotine replacement therapy. Full scale randomised controlled trials could lead to widespread adoption of this drug which, because of its cost, could make effective treatment available to millions of smokers that would otherwise not be able to afford it.

Introduction

Nicotine replacement therapy and bupropion increase 12-month continuous abstinence rates of smokers making a quit attempt by 5-14% depending on the context (1-3). Other medications have also been found to aid cessation, most notably nortriptyline (2). New medications in the pipeline are varenicline (Pfizer) (4) and rimonabant (Sanofi-Aventis) (5). Nicotine vaccines are undergoing clinical trials (6). Behavioural support, can improve the chances of success of quit attempts by an estimated 2-7% (7-9).

The cost of smoking cessation treatments is an important issue. The cost per life year gained compares very favourably with other medical treatments but most healthcare systems and many smokers, even in richer countries, do not feel that they can afford the current forms of treatment. If a much cheaper form of treatment exists that is as effective, it is important to evaluate it. One such medication is Tabex (10-12). The active ingredient of Tabex is cytisine (1.5 mg in each tablet). The cost for a full course of treatment in Poland is approximately the equivalent of £6 (US\$10) and in Bulgaria it is about £2.50 (US\$ 5) (for more information see: www.bpg.bg/tabex). This drug has been licensed for over 40 years in Eastern and Central Europe and many smokers in Poland use it. The total sales of Tabex in 2004 exceeded 1 million courses. It has been subjected to Phase I and Phase II studies and clinical trials (see below). However, it has not been subjected to sufficiently rigorous evaluation according to modern standards and would not receive a licence if submitted for approval today.

Cytisine is a compound derived from the plant, *Cytisus laburnum*. It is a nicotinic partial agonist binding with high affinity to a number of different subtypes of the neuronal nicotinic receptors, including receptors composed of α_4 and β_2 subunits (13, 14) which are believed to be central to the effect of nicotine on the reward pathway (see 4). Because it has a high affinity for the receptor cytisine prevents other ligands such as nicotine from attaching to it. However, its effect once attached to the receptor is much less than that of nicotine. As a result, the drug would be expected to reduce the rewarding effects of nicotine and to decrease craving and attenuate nicotine withdrawal symptoms but not itself to be addictive or provide positive reward. Despite its properties there is no dissemination of the drug in western countries. However cytisine has provided the starting point for a new medication for smoking cessation, varenicline, that has recently undergone clinical trials (4).

Pharmacokinetic data derive mainly from animal studies (15, 16). Applied orally in rabbits, cytisine is well absorbed in the gut. The elimination half-life after oral administration is 52 minutes. The drug is mainly excreted in unchanged form with the urine. Phase I studies show that cytisine has pharmacological effects that are somewhat similar to those of nicotine. Its toxicity is broadly similar though somewhat less (4, 5, 15, 16). Clinical studies show that Tabex is well tolerated at the doses applied (17). Where side effects do occur, these include: changes in both taste and appetite, dryness in the mouth, headache, irritability, nausea, constipation, tachycardia, and mild elevation of the arterial blood pressure (10-12).

As regards efficacy, in one study reported in the documentation supporting registration in Poland, 366 smokers with 'chronic bronchitis' were given Tabex and compared with 239 patients treated with placebo (17). Patients were smokers having a serious intention to stop smoking. At 8-week follow-up, 55% of patients receiving

Tabex were reported abstinent compared with 34% on the placebo ($p < .05$). However, abstinence was not adequately defined and allocation was not random. Another study was a randomised placebo-controlled trial of 1214 smokers followed up for 2 years (18). Follow-up was by post and reported abstinence rates were 21% in the active versus 13% in the placebo group ($p < .001$). Another placebo-controlled trial was carried out in the Federal Republic of Germany in which 2470 smokers were allocated to receive one of 16 drugs of whom 520 were treated with Tabex or placebo. After 3-months 25% of those on Tabex reported abstinence in a postal questionnaire compared with 21% on placebo ($p > .05$) (19). It was not clear how smokers were assigned to conditions.

No serious adverse effects were reported in the trials but the documentation and design of these studies would not be considered sufficient to support registration in European countries because of, amongst other things, lack of longer-term follow-up, clear definitions of sustained abstinence and absence of biochemical verification. However, the data do suggest that the drug is safe and efficacious. There is a need to undertake a rigorous evaluation of its safety and efficacy using outcome criteria that are widely accepted in the field.

As a first step to this, we have undertaken an open label uncontrolled trial of use of the drug in a smokers clinic in Warsaw. Smokers attending the clinic were prescribed the recommended course of treatment and followed up using Russell Standard criteria for 12 months. If 12-month continuous abstinence rates were observed that were substantially higher than the figure of 2-10% seen in placebo groups of other clinical trials (1) or in smokers attempting to stop unaided (20), there would be a strong prima facie case for effectiveness and this would merit moving rapidly to full scale placebo-controlled randomised controlled trials. In an evaluation of the UK stop smoking services, a programme of weekly behavioural support for 4 weeks after the quit date plus NRT or bupropion yielded a continuous 12-month abstinence rates of 15% verified by carbon monoxide test (21). Clinical trials of nicotine replacement therapies with minimal support may provide a better comparison point because in the present trial, smokers usually only received one session of behavioural support. The >6 month continuous abstinence rates in the active treatment group of these NRT trials was 14% (1). An abstinence rate similar to this would suggest therapeutic efficacy.

Methods

This was an open, uncontrolled trial in the form of a clinical audit. A total of 438 consecutive attendees at the stop smoking clinic at the cancer institute in Warsaw between 17 November and 27 December 2003 took part. The stop smoking clinic provides a service to the local community and is provided free of charge. Smokers were considered for admission into the trial if they were seeking help with stopping smoking at the clinic. Smokers were excluded if they were judged by the consulting physician to be contra-indicated for Tabex. The exclusion criteria were: active stomach ulcer, uncontrolled hypertension, adrenal hypertrophy, receiving treatment for a psychiatric disorder. Two smokers were excluded by these criteria. Eligible patients were informed about the study and provided verbal consent. A total of 436 patients were included.

The treatment programme consisted of one session prior to quitting and the offer of other sessions to those that wanted it. The main session involved a nurse collecting

demographic information and measuring blood pressure, heart rate, height, weight, and expired-air carbon monoxide concentration (CO). The patients then completed a questionnaire on nicotine dependence (FTND, 22). Then the patient was seen by a physician who took a smoking and medical history and obtained informed consent from eligible patients. The physician provided information about Tabex, including the usage regimen and side effects. Patients then received individually tailored advice on stopping smoking and written support materials. Patients were offered follow-up visits as required by the patient. The session lasted approximately 30 minutes in total. Follow-up visits, where they occurred, lasted about 20 minutes and did not follow a formal structure.

Tabex is administered orally in a dose of 1 tablet every 2 hours (6 tablets daily) for 3 days while smokers reduce of the number of smoked cigarettes. The treatment then proceeds according to the following scheme: from the 4th to 12th day - 1 tablet every 2.5 hours (5 tablets daily); from the 13th to 16th day - 1 tablet every 3 hours (4 tablets daily), from 17th to 20th 1 tablet every 4 hours (3 tablets daily), from the 21st to 25th day - 1 tablet every 6 hours, 1-2 tablets daily. Smokers were instructed that they should have stopped smoking completely by the 5th day. The average duration of taking medication was 22 days. The duration of the course of medication was shorter than for medication such as bupropion or nicotine replacement therapies but this was a clinical audit of the treatment regimen currently licensed and it would not have been appropriate operate outside the licence.

Participants were followed up at 12 weeks with up to one additional week needed to make contact. Those who reported being abstinent at 12 weeks were followed up at 12 months with up to an additional 2 months needed to make contact. The 12 week follow up involved only telephone contact. Participants were asked whether they were currently smoking and whether they had smoked at all since the quit date, how far they had followed the treatment regimen and about any adverse events. The 12 month follow up involved an initial telephone contact; participants who reported that they had not smoked since the 12-week follow up were invited to attend the clinic for CO verification. Participants who were unable to attend the clinic were offered a home visit.

Outcome was assessed using the Russell Standard (23). This standard is designed to facilitate comparison of outcome figures across studies. It involves 12-months of continuous abstinence recorded at the 12-month follow-up and supported at that follow-up by an expired air-carbon monoxide (CO) of less than 10ppm. The Russell Standard allows reporting of up to 5 cigarettes during the follow-up window but in the present study only reports of complete abstinence were counted as successes. All smokers allocated to receive the treatment are included in the analysis and any participants that cannot be followed up are considered to have resumed smoking.

Results

Table 1 shows the sample characteristics. The participants were similar in smoking and demographic profile to those found in clinical trials in the US and UK (see 1). Their FTND (dependence) score was slightly higher than that found in other clinical studies or the average for smokers attending the UK stop smoking services (21). However, the smokers had started smoking at a slightly older age than is typically found in US and UK studies. The majority of participants attended just one session.

Table 1: Sample characteristics and outcome

Total attending clinic	438
Number excluded	2
Total enrolled	436
Percent (N) males	43.8 (191)
Mean (SD) age	44.4 (13.1)
Percent (N) smoking more than 10 cigarettes per day	95.0 (414)
Percent (N) smoking more than 20 cigarettes per day	51.6 (225)
Mean (SD) FTND score (dependence)	6.1 (2.2)
Percent (N) with post-secondary education	26.8 (117)
Mean (SD) age of starting to smoke regularly	18.9 (4.5)
Percent (N) having tried to quit before	70.2 (306)
Percent (N) attending 1 session	54.1 (236)
Mean (SD) number of visits to clinic	1.7 (0.9)
Number followed up at 12 weeks	342
Number of those followed up who reported taking ≥ 1 dose of medication	315
Percent (N) abstinent at 12 weeks	27.5 (120/436)
Percent (N) reporting gastric disturbance/nausea	10.4 (33/315) ¹
Percent (N) stopping medication due to adverse events	15.5 (49/315) ¹
Number attempted to follow up at 12 months	120
Number followed up at 12 months	112
Number reporting abstinence	68
Percent (N) confirmed abstinent at 12 months by CO	13.8 (60/436)

¹The number reporting having taken medication

Three-hundred and forty-two smokers were successfully followed up by telephone at 12 weeks. Of these 315 indicated that they had taken at least one tablet of Tabex. One hundred and twenty participants (27.5%) of the total sample reported having not smoked at all since the quit date. When these participants were followed up at 12 months, 60 (13.8% of the original sample) reported having been abstinent for the preceding 12 months and were confirmed as abstinent by CO at the follow up.

A total of 13.8% of those attending the smokers' clinic reported being continuously abstinent for 12 months at follow-up with their current smoking status confirmed by expired air carbon monoxide concentration. It may be noted that there were 27 participants who reported at follow up that they had not taken any medication and all of these had returned to smoking and that all participants (98) who could not be contacted were assumed to be smoking.

At the 12-week follow up patients were asked about known nicotine withdrawal symptoms using a check list and any other adverse events using an open response format. The most frequently reported withdrawal symptoms were: irritability (36%), restless (23%), depression (15%), appetite increase (47%), sleep disturbance (21%). Constipation occurred in less than 10% patients but they were more frequently observed among those who quit (13% vs. 6%). The most frequently reported adverse events were: dryness in the mouth (35%), nausea and gastric disturbances (10%). Of

the 315 subjects, who had taken the drug, 49 (15.5%) reported that they stopped due to adverse effects, 31 due to nausea and gastric disturbances.

Discussion

The 12-month success rate was similar to the figure observed in the evaluation of the UK smoking cessation services. This was despite the fact that the smokers were more dependent on average as indexed by the FTND and most only attended one session of psychological support.

There may be many reasons for the high success rate in the Polish study other than treatment using Tabex, but the absolute percentage figure, together with clinical data used to register the product, give strong *a priori* grounds for believing that the drug is effective. The 6-month sustained quit rates of the placebo group in NRT trials involving minimal behavioural support is 8% (1) but there were studies that had higher rates than this, so we cannot rule out a placebo response or chance as leading to the relatively high success rates in the present study.

There were no reported serious adverse events. The numbers reporting minor adverse events was higher than the figure for nicotine replacement therapies. However, without a direct comparison caution should be exercised in interpreting this figure.

Taken together with the results from earlier studies these findings support the argument for a drug evaluation programme undertaken to modern standards. This would include large scale clinical trials of this drug to a standard that would be acceptable by regulatory authorities around the world. More information is also required on pharmacokinetics properties of the drug, its safety profile and ideally studies varying the dose and the duration of dose. The obvious advantage of this medication is its cost. It offers the prospect of providing access to effective treatment to help with smoking cessation to millions of smokers who would not otherwise be able to afford it. For healthcare providers it offers the prospect of hugely reduced costs.

If Tabex is found to be more effective than placebo, the question will arise as to whether it is similar in effectiveness to other medication on the market or likely to become available soon such as varenicline. At the time of writing there have been no published reports on the effectiveness of varenicline but data presented at conference papers appear to show superiority over bupropion with one-year continuous abstinence rates of more than 20%. The mode of action of Tabex is similar though the duration of treatment, precise pharmacology and dosing regimen may all lead to differences in effectiveness. A comparison between varenicline and Tabex may be worthwhile if placebo controlled trials show Tabex to have some efficacy.

Acknowledgements and competing interest statements

Witold Zatonski – none declared
Magdalena Cedzyska – none declared
Piotr Tutka – none declared

Robert West has undertaken research and consultancy for companies that develop and manufacture smoking cessation medications. He is part funded by Cancer Research UK.

We would like to express our thanks to Sopharma for supplying the Tabex.

We would like to thank, as well, all staff members who worked daily in the clinic – doctors: Elzbieta Karpinska, Dorota Lewandowska, Joanna Jonska, Joanna Surowinska, Ewelina Bobek-Pstrucha, and nurses: Katarzyna Marczyk, Dorota Sadowska, Zofia Kociszewska.

Contributors

Witold Zatonski – overall concept of the trial, planning, preparation and supervision of work done in trial, participation in analysis and editing the paper.

Magdalena Cedzynska – participation in planning the observation, everyday controlling works doing in clinic, participation in analysis data and editing the paper.

Piotr Tutka – participation in drafting and editing the paper.

Robert West – participation in designing the follow-ups, analysis and drafting and editing the paper.

This study was a clinical audit and there was not at that time regulation in Poland to submit this kind of research to ethics committee. The manufacturer of the drug provided it free to the clinic but did not have any say on methods and data analysis.

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