Evidence for the use of appetite suppressant drugs in Brazil: a pharmacoeconometric study

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SUMMARY

Objective: Analyze the use of appetite suppressants in Brazil in 2009, according to the characteristics of users, healthcare system, and other drugs. Methods: Pharmacoeconometric study of cross-sectional data to analyze the relationship between the use of appetite suppressants (mg/per capita) and the independent variables selected (gender, race/color, age, schooling, income, health insurance coverage, and use of fluoxetine and chlordiazepoxide) using multiple linear regression analysis. This study used these variables in level of aggregation by states for 2009. The analyses were performed using the Gretl software. Results: We highlight that São Paulo showed the highest use of appetite suppressants with 97.3 mg/per capita, followed by Goiás with 94.8 mg/per capita. The lowest use of appetite suppressants was seen in Ceará (3.8 mg/per capita). The biggest fluoxetine users were in Rio Grande do Sul, with 58.0 mg/per capita, and in Goiás, with 51.5 mg/per capita. Ceará showed the lowest fluoxetine use (2.3 mg/per capita). For chlordiazepoxide, the highest values were seen in Minas Gerais (7.5 mg/per capita) and in Rio de Janeiro (4.8 mg/per capita), while Amazonas (0.08 mg/per capita) showed the lowest use. Based on regression analysis, we can highlight: 1) the use of appetite suppressants is related to income, education, and fluoxetine use; and 2) race/color, gender, age, health insurance coverage, and use of chlordiazepoxide showed no relation to the use of appetite suppressants. Conclusion: These evidences may contribute to the improvement of regulatory actions, sanitary surveillance, and ethical conduct, particularly with regard to the concomitant use of appetite suppressants and fluoxetine, which is prohibited by the Federal Council of Medicine (Conselho Federal de Medicina) and also by National Health Surveillance Agency (Anvisa –Agência Nacional de Vigilância Sanitária).

Keywords: Regression analysis; appetite suppressants; pharmaceutical economics; obesity.
EVIDENCE FOR THE USE OF APPETITE SUPPRESSANT DRUGS IN BRAZIL: A PHARMACOECONOMETRIC STUDY

INTRODUCTION

Little is known about the correlation between the use of appetite suppressant drugs and other sociodemographic and health care variables. This is a serious issue because obesity is considered a public health problem due to the increased prevalence worldwide. This health condition, which is included in the group of non-transmitted chronic diseases, can be defined as the excessive accumulation of body fat in such a way that it brings health damage to people.

Since 1980, the prevalence of obesity has increased three times or more around the world, probably due to changes in dietary habits and lifestyle. An analysis of epidemiological studies performed by Farrigan and Pang indicates that the prevalence of obesity in countries with the largest pharmaceutical market (United States, France, Germany, Italy, Spain, United Kingdom, and Japan) was estimated, on average, as 3.8% annually along 10 years (2000 through 2010), while in countries like Brazil this growth in the same period was 5.5%. Then an estimate was made showing that the number of obese adults in the seven main pharmaceutical markets (United States, France, Germany, Italy, Spain, United Kingdom, and Japan) grew from 95 million in 2000 to 139 million in 2010. Furthermore, less than 25% of potential patients are formally diagnosed as obese; among these, less than 20% are treated with pharmacological therapy.

Another projection made by the World Health Organization (WHO) points out that in 2015, approximately 2.3 billion adults will be overweight and more than 700 million will be obese. The United States are currently the largest market selling anti-obesity drugs, having around 68% of its population overweight or obese, followed by the United Kingdom and other European countries. However, China, Russia, India, and Brazil may soon start to match the western countries in terms of their obese populations. For example, obesity in China and levels of excessive weight are foreseen to reach 665 to 670 million individuals by 2015.

Data published by the Ministry of Health show an increasing frequency of people who are overweight and obese in Brazil. In 2006, the percentage of individuals who were overweight was 42.7% and in 2010 this amount went up to 48.1%. Regarding obese people, this variation ranged from 11.4% (2006) to 15.0% (2010).

The objective of this work was to analyze the use of appetite suppressants which are under the Administrative rule SVS/MS N. 344/1998 in Brazil in 2009, according to the characteristics of users (gender, age, education, income, and race/color), healthcare system (health insurance coverage rate), and use of fluoxetine (antidepressive) and chlor Diazepoxide (anxiolytic). Literature data indicate that fluoxetine and chlor Diazepoxide were the drugs most associated with concomitant use of appetite suppressants.

METHODS AND HYPOTHESES

Pharmacoeconometric study of cross-sectional data to analyze the relationships between the use of appetite suppressants and variables, such as gender, race/color, age, income, health insurance coverage, and use of fluoxetine and chlor Diazepoxide, using an econometric model for a multiple linear regression analysis. The study used these variables in a level of aggregation per units of the federation (UF) referring to 2009; data collection was performed between March and April, 2011.

The econometric model established was:

\[ CMA_1 = \beta_1 FEM_1 + \beta_2 RAC_1 + \beta_3 IDA_1 + \beta_4 ESC_1 + \beta_5 REN_1 + \beta_6 TCP_1 + \beta_7 CFL_1 + \beta_8 CCL_1 + u_1 \]
- CMA \_i \_ - Use of appetite suppressant drugs in milligrams (mg)/per capita, represented by the active ingredients amphetamine, fenproporex, mazindol, and sibutramine sold in the Brazilian pharmaceutical market in industrialized and magistral formulations per unit of the federation. The population with an indication for taking these drugs (aged 18 to 64 years) was used to calculate the per capita use of appetite suppressant drugs.
- FEM \_i \_ - proportion of women per unit of the federation (UF).
- RAC \_i \_ - proportion of white individuals per UF.
- IDA \_i \_ - proportion of individuals aged 60 years or older per UF.
- ESC \_i \_ - ratio of individuals aged 25 years or older with 15 or more years of schooling.
- REN \_i \_ - average monthly family income per capita in Brazilian Real of the 10% richest people per UF.
- TCP \_i \_ - health insurance coverage rate in percentage per UF.
- CFL \_i \_ - use of fluoxetine, in mg/per capita, sold in industrialized and magistral formulations per UF.
- CCL \_i \_ - use of chlordiazepoxide, in mg/per capita, sold in industrialized and magistral formulations per UF.
- \( u_i \) - represents the stochastic error of the model estimate.

To calculate the use in mg/per capita of fluoxetine and chlordiazepoxide we used the same age group of the population of the appetite suppressant drugs.

The database was formed from different sources of evidence available. Such sources were the determining factor in choosing the year 2009, as for the preceding and subsequent years it was not possible to gather the values for all the variables studied. Thus, the values of the FEM, RAC, IDA, ESC, and REN variables were obtained from the National Research of Samples by Domiciles (Pesquisa Nacional de Amostras por Domicílios – PNAD) from 2009, published by IBGE (Brazilian Institute for Geography and Statistics). The data from TCP were collected in the Supplementary Health National Agency (Agência Nacional de Saúde Suplementar – ANS) website, while the CMA, CFL, and CCL values were extracted from the SNGPC database, from Anvisa. SNGPC is a sanitary surveillance information system which captures data on purchase and sale of drugs under Administrative rule SVS/MS N. 344/1998, using XML files. Up to 2009, there were 35,031 pharmacies/drugstores accredited at SNGPC spread among 3,494 Brazilian municipalities, which sent 3,175,863 XML files to Anvisa's system base.

Descriptive statistical analysis was used to calculate measures of central tendency and dispersion. The degree of linear association between the independent variables was evaluated by calculating the correlation coefficient. A model of multiple linear regression was estimated with all the variables studied and validated in terms of heteroscedasticity (White's test) and colinearity (variance inflation test, VIF). All analyses were performed with the Gretl software.

Because this research is based on database records (secondary data) publicly available or obtained through institutional contact and maintains the anonymity of the interviewees, submission to the Research Ethics Committee was not necessary.

The hypotheses to be tested in the econometric model are described below with their respective arguments.

**H1: CMA IS HIGHER AMONG WOMEN**

Data reported by Cawley and Rizzo\(^1\), suggest that sociological and psychology studies consider obesity more associated with low self-esteem in women than in men, as well as the existence of a greater social stigma for women. Khan et al.\(^12\), in a study to estimate the prevalence of use of prescription drugs for weight loss, found that the use of these products was more common among women than men. In Brazil, a study performed by Carneiro, Guerra-Júnior, and Acúrcio\(^13\) in Belo Horizonte evidenced the absolute predominance of the use of these drugs by women in relation to men in a ratio of 10:1.

**H2: CMA IS HIGHER AMONG WHITE PEOPLE**

According to Cawley and Rizzo\(^1\), there are distinct differences regarding the use of weight loss drugs between races/color. In this study, we assume that white race/color individuals are more prone to use appetite suppressant drugs in the country.

**H3: CMA DECREASES WITH AGE**

According to Cawley and Rizzo\(^1\), the main reason for the CMA is becoming physically attractive. For people outside the fertile age, the social cost of not being attractive may decrease. Although the consequences of obesity worsen with age, the authors suspect that such situation contributes to these people having a bigger concern for the use of drugs destined to treat comorbidities (type II diabetes, dyslipidemia, hypertension), instead of obesity.

**H4: CMA INCREASES WITH EDUCATION**

According to Grossman and Kaestner, quoted by Cawley and Rizzo\(^1\), education is strongly correlated to good health, as it leads people to choose a better-input mix and use it in a more efficient way for producing health. Thus, people with higher education degree are more prone to the CMA. A study of Spanish data indicates that the probability of an individual using medication is higher as his level of education increases\(^13\).
H5: CMA INCREASES WITH INCOME
As proposed by Cawley and Rizzo\(^1\), we also assume that appetite suppressant drugs are considered a normal asset. So, by keeping other variables constant, we see that with an increased income people tend to buy more of these drugs.

H6: CMA IS HIGHER AMONG INDIVIDUALS WITH HEALTH INSURANCE
Administrative rule SVS/MS N. 344/98 determines that the drugs which are the object of this study can only be sold with their prescription retention in the pharmaceutical establishment and with the bookkeeping in the SNGPC\(^8,9\). Thus, the first stage for the use of appetite suppressants drugs is that the patient be seen by a doctor. In this sense, people who have health insurance in Brazil have a better access to this professional and, consequently, it might be easier for them to acquire such products.

H7: CMA IS POSITIVELY CORRELATED TO THE USE OF FLUOXETINE OR CHLORDIAZEPoxide
According to Carneiro, Guerra-Júnior and Acúrcio\(^10\), among patients who received anorexigenics, 91.8% had a prescription for the concomitant use of another substance, with fluoxetine and chlordiazepoxide as most associated drugs.

RESULTS
The descriptive analyses of the variables studied are shown in Table 1. We can notice that for some variables, such as CMA, RAC, TCP, and CFL, there is a greater variability among their minimum and maximum values.

The state of São Paulo had the highest CMA, 97.3 mg/per capita, followed by Goiás, with 94.8 mg/per capita. The lowest use was verified in Ceará (3.8 mg/per capita). The highest proportion of women was seen in the Federal District, Pernambuco, and in Rio de Janeiro, all with 53%, while Amapá (49.0%) and Tocantins (49.0%) presented the lowest proportions.

The southern region states presented the highest proportions of individuals who claimed to be of the race/white color in the following decreasing order: Santa Catarina (85.7%), Rio Grande do Sul (81.3%), and Paraná (71.8%). The lowest proportions of white individuals were registered in Amazonas (21.2%) and Bahia (21.8%). In relation to the proportion of individuals aged 60 years or older, the states of Rio de Janeiro (15.0%) and Rio Grande do Sul (13.7%) were the first and second, respectively, while Roraima (4.8%) was the state with the lowest proportion of individuals in this age group.

The highest proportion of individuals aged 25 years or older with 15 or more years of education was found at the Federal District (23.0%) and Rio de Janeiro (13.8%), while the state of Maranhão showed the lowest proportion (4.2%). The average monthly family income per capita of the richest 10% were found in the Federal District (R$ 7,987.92) and in Rio de Janeiro (R$ 4,496.49). The state of Alagoas presented the lower income (R$ 1,846.56).

The state of São Paulo (40.4%) and Rio de Janeiro (33.8%) presented the highest rates of health insurance coverage, while Maranhão (4.7%) had the lowest rate. The states with the highest consumption of fluoxetine were Rio Grande do Sul with 58.0 mg/per capita and Goiás with 51.5 mg/per capita. Ceará (2.3 mg/per capita) registered the lowest consumption of this drug. For chlordiazepoxide, the highest consumption was found in Minas Gerais (7.5 mg/per capita) and Rio de Janeiro (4.8 mg/per capita), while Amazonas (0.08 mg/per capita) showed the lowest consumption.

The correlation coefficients between the independent variables are presented in Table 2. There is a high and positive correlation between the CFL and RAC variables (0.8116) and also between the REN and ESC variables (0.9590), that is, these variables move in the same direction and with a high linear association degree. The remaining variables do not present values > 0.80,

Table 1 – Values of the measurements of central tendency and dispersion of studied variables, Brazil, 2011 (n\(^o\) of observations = 27)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean ± SD</th>
<th>Median (min-max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMA (mg/per capita)</td>
<td>39.4 ± 31.9</td>
<td>28.1 (3.8-97.3)</td>
</tr>
<tr>
<td>FEM (%)</td>
<td>51.0 ± 0.9</td>
<td>51.0 (49.1-53.0)</td>
</tr>
<tr>
<td>RAC (%)</td>
<td>39.2 ± 18.2</td>
<td>36.3 (21.2-85.7)</td>
</tr>
<tr>
<td>IDA (%)</td>
<td>9.8 ± 2.4</td>
<td>10.3 (4.8-15.0)</td>
</tr>
<tr>
<td>ESC (%)</td>
<td>9.2 ± 0.6</td>
<td>8.7 (4.2-23.0)</td>
</tr>
<tr>
<td>REN (R$)</td>
<td>2,981.70 ± 1,211.50</td>
<td>2,662.70 (1,845.60-7,987.90)</td>
</tr>
<tr>
<td>TCP (%)</td>
<td>14.6 ± 9.0</td>
<td>10.8 (4.7-40.4)</td>
</tr>
<tr>
<td>CFL (mg/per capita)</td>
<td>22.0 ± 18.1</td>
<td>15.4 (2.3-58.0)</td>
</tr>
<tr>
<td>CCL (mg/per capita)</td>
<td>1.8 ± 1.8</td>
<td>1.2 (0.08-7.5)</td>
</tr>
<tr>
<td>SD, standard deviation.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
which means there is no linear association. It is noteworthy that no correlation was found to be negative among the studied variables.

The econometric model was estimated by minimal ordinary squares, considering the variables previously described for the 27 units of the federation in Brazil. The model results are shown in Table 3.

The results of the estimated econometric model showed that when all independent variables are equal to zero, the CM will be 111.65 mg/per capita. The angular coefficients estimated for ESC, REN, and CFL were statistically significant, according to statistical values of p-value in Table 3. However, angular coefficients ESC and CFL showed to be coherent with the hypotheses raised by the study. By the value of the ESC angular coefficient, one can say that an increase of 1% in ESC produces an increase of 6.46 mg/per capita in CMA. Similarly, an increase of 1 mg/per capita in CFL produces an increase of 1.66 mg/per capita in CMA.

The angular coefficient of the IDA and TCP variables were estimated with a correct signal; that is, they comply with the study hypothesis, but were not significantly different from zero. It is also worth highlighting that approximately 85% of the variations in CMA by unit of the federation can be explained by the eight previous variables together, incorporated into the econometric model, as well as the constant and the angular coefficients together are statistically different from zero with 5% significance (p-value(F) < 0.0001).

According to the VIF, there is a problem of colinearity between the ESC (18.06) and REN (16.05) variables. For the remaining variables, the VIF values ranged from 1.90 for FEM to 5.37 for CFL, which means there are no perfect linear relations. Through White’s test (p = 0.126486), the model’s variance is constant, that is, there is no heteroscedasticity.

**DISCUSSION**

According to our literature review, this is the first pharmacoecenometric study performed in Brazil that explores the correlation between the use of appetite suppressant drugs and sociodemographic and health care variables, analyzed from an econometric model. There is a scarcity of national studies using the econometric method to assess the correlation between the use of drugs and important variables that may influence, decreasing or increasing such need of the country’s population.

Independent variables adopted in the econometric model sought to explicitly incorporate, for the studied

**Table 2 – Linear association between the independent variables studied, Brazil, 2011 (n of observations = 27)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>Standard error</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEM</td>
<td>1.0000</td>
<td>0.2567</td>
<td>0.3216</td>
</tr>
<tr>
<td>RAC</td>
<td>1.0000</td>
<td>0.4935</td>
<td>0.6022</td>
</tr>
<tr>
<td>ESC</td>
<td>1.0000</td>
<td>0.4348</td>
<td>0.4023</td>
</tr>
<tr>
<td>IDA</td>
<td>1.0000</td>
<td>0.6136</td>
<td>0.9590</td>
</tr>
<tr>
<td>TCP</td>
<td>1.0000</td>
<td>0.1335</td>
<td>0.1356</td>
</tr>
<tr>
<td>REN</td>
<td>1.0000</td>
<td>0.0564</td>
<td>0.6947</td>
</tr>
<tr>
<td>CFL</td>
<td>1.0000</td>
<td>0.5640</td>
<td>0.3562</td>
</tr>
<tr>
<td>CCL</td>
<td>1.0000</td>
<td>0.5536</td>
<td>0.4237</td>
</tr>
</tbody>
</table>

**Table 3 – Results of regression equation 1, Brazil, 2011**

<table>
<thead>
<tr>
<th>Dependent variable: CMA</th>
<th>Coefficient</th>
<th>Standard error</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>111.65</td>
<td>180.84</td>
<td>0.5447</td>
</tr>
<tr>
<td>FEM</td>
<td>-173.27</td>
<td>373.18</td>
<td>0.6480</td>
</tr>
<tr>
<td>RAC</td>
<td>-30.77</td>
<td>31.11</td>
<td>0.3359</td>
</tr>
<tr>
<td>ESC</td>
<td>6.46</td>
<td>2.81</td>
<td>0.0338*</td>
</tr>
<tr>
<td>IDA</td>
<td>-1.97</td>
<td>1.81</td>
<td>0.2899</td>
</tr>
<tr>
<td>TCP</td>
<td>0.80</td>
<td>0.53</td>
<td>0.1484</td>
</tr>
<tr>
<td>REN</td>
<td>-0.02</td>
<td>0.008</td>
<td>0.0263*</td>
</tr>
<tr>
<td>CFL</td>
<td>1.66</td>
<td>0.31</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>CCL</td>
<td>-0.94</td>
<td>2.05</td>
<td>0.6517</td>
</tr>
</tbody>
</table>

N of observations: 27

Adjusted R²: 0.84727

*Statistically significant with 95% confidence.
aggregated level, elements that the analysis assumes as determinants for the use of appetite suppressant drugs in 2009 in the units of the federation. In this sense, in the estimated econometric model, the variable with the highest power of explaining the variation in the use of appetite suppressant drugs is the use of fluoxetine.

The study shows that 91.8% of patients who received anorexigenics were also concomitantly prescribed some other substance, with fluoxetine and clordiazepoxide as the most associated drugs. Carlini et al. indicate that fluoxetine is used as suggestive for weight loss, and not for treating depression. These findings suggest that the concomitant use of appetite suppressant drugs and fluoxetine is being used as means to obtain more effectiveness in the treatment of obesity or weight loss in a shorter period of time. However, in a metaanalysis study, a bidirectional association between depression and obesity was observed, that is, obese people had a 55% increased risk of developing depression over time, while depressed people had a 58% higher risk of becoming obese. The association between depression and obesity was stronger than the association between depression and overweight, which reflects a dose-response gradient.

Studies refer to a higher prevalence of drug use for weight loss among women. Regarding race/color, a study published by Cawley and Rizzo showed that there are discrepant differences related to the use of appetite suppressant drugs among race/color, gender, and individuals with health insurance. The authors found that African-American individuals are considerably less prone to use appetite suppressant drugs, which arouses concern because obesity rates are higher among this group of people. In Brazil, the prevalence of overweight and obesity was higher among black women, which can be related to the difficulty this population has to access different treatment modalities, including appetite suppressant drugs. In our study, a group of individuals of all ages in FEM and RAC variables may be an explanation for obtaining a signal that is not coherent with the definition of the study hypotheses which deserves further research including individuals aged ≥ 18 years in the econometric model.

Regarding the REN variable, the coefficient signal was also not coherent with the study hypothesis. A possible explanation is that this portion of the Brazilian population has more advantaged economic conditions which allow them to have access to other obesity treatment modalities, such as bariatric surgery and a diet supervised by a skilled professional. In Brazil, the Household Budget Survey (HBS) performed in 2002-2003 evidenced a direct association between obesity and family income for men, and among the women of the highest income group the obesity prevalence was lower. Migh these findings indicate that lower income women have searched for several obesity treatment modalities, such as the use of appetite suppressant drugs? A population-based study performed in Pelotas (Brazil) shows that more than 1% of the population has used some amphetamine derivative over the past two weeks, and the use of such drugs as appetite suppressants was higher among women in high education and income groups. As to the collinearity among the ESC and REN variables, the literature evidences that income increase is strongly related to the number of years that individuals have studied.

The angular coefficient of IDA and TCP variables, although estimated with a correct signal, that is, they fulfilled what was proclaimed by the study hypothesis, in our econometric model, do not influence the use of appetite suppressant drugs in the UF. Data published by the Ministry of Health indicate that for both genders overweight frequency, as well as the number of obese people, tends to grow with age.

In Brazil, the use of amphetamine derivatives (amphetamine, fenproporex and mazindol) has fallen from over 6.97 the defined daily dose (DDD)/thousand inhabitants/day in 1993-1995 to 2.27 DDD/thousand inhabitants/day between 1997 and 1999. However, after this period, the use has reached the amount of 9.1 DDD/thousand inhabitants/day in the biennial 2002-2004. A retrospective study performed in the city of Belo Horizonte, in Minas Gerais, showed an estimated use of 19.75 DDD/thousand inhabitants/day in 2003. Another study also conducted in Belo Horizonte, in 2002, found an amphetamine derivatives use of 15 and 18 DDD/thousand inhabitants/day, in the first and second semesters, respectively. In subsequent years, Brazil became known as the world champion in the use of slimming drugs. However, data published by Anvisa revealed a significant reduction in the use of appetite suppressant drugs by the Brazilian population in 2009. The DDD/thousand inhabitants/day for amphetamine, fenproporex, and mazindol was 0.61, 0.62, and 0.035, respectively. The use of sibutramine was 2.78 DDD/thousand inhabitants/day.

For Carneiro, Guerra Júnior, and Acúrcio, the gold standard of weight-loss formulas is formed by an anorexigenic, an anxiolytic and a laxative. In our study, the coefficient of the clordiazepoxide drug use variable presented a signal that is contrary to the study hypothesis, but it is not statistically significant. Obesity in women is associated with the use of anxiolytics, antidepressives, sleep disturbances, and low level of life satisfaction.

We believe that an analysis of data in a municipal aggregation level may establish new variables that are statistically significant and coherent in terms of logical signal, as indicated by evidences available in the literature, as well as the inclusion of other variables, such as obese population and people who are overweight associated with...
comorbidities (e.g., psychiatric problems). Such variables would be important in the econometric model to answer the following question: Is the process of prescription-indication of appetite suppressant drugs in the country a rational one?

An important point for pharmacoeconomics studies is the precision of data to be inserted in the model aiming at an adequate statistical inference. In our study, the sales data of the appetite suppressant drugs were used as a proxy for these drugs consumption in the country. The SNGPC keeps accounts of the use of drugs sold in private pharmacies/drugstores, while some chains of these establishments, by a court order, do not send the balance of buying and selling to the system. Two other important points that interfere with the estimate of the use of the studied drugs are: 1) operational problems at SNGPC may have along the year prevented the receipt of XML files containing the balances of buying and selling of drugs; 2) as these products many times are the object of interest for illicit sales, some physical units used by part of the populations may not have been captured by SNGPC.

The empirical evidences arising from this study may contribute to improve regulatory actions, sanitary surveillance, and ethical conduct, reviewing and amplifying the discussion of the concomitant use of these products with fluoxetine, which is prohibited by a resolution issued by the Federal Council of Medicine, besides being prohibited by a norm published by Anvisa.

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