USE OF MONOAMINE OXIDASE INHIBITORS FOR THE MANUFACTURE OF DRUGS INTENDED FOR THE TREATMENT OF OBESITY

The present invention relates to the use of monoamine oxidase inhibitors in the manufacture of drugs intended for the treatment of obesity.

Obesity is a major health problem in western societies and its prevalence is increasing. As described in Cheryl P. Kordik and Allen B. Reitz, *J. Med. Chem.* (1999), **42**(2), 181-201, reviewing the various known strategies to treat obesity, obesity is a "chronic condition characterized by overabundance of adipose tissue" which "correlates with risks such as high blood pressure, coronary heart disease, diabetes, altered steroid metabolism, gallstones and certain forms of cancer".

Obesity is a multifactorial disease and its treatment requires multidisciplinary approaches. The treatment includes diet, exercise, behavior change, pharmacotherapy, and surgery. In the medical treatment of obesity, different approaches may be considered. Drugs may decrease energy intake (central or peripheral action), decrease energy storage, increase energy expenditure, or have a combination of different actions. A few compounds are currently available in some countries. These include sibutramine (a serotonin and norepinephrine reuptake inhibitor) and orlistat (a pancreatic lipase inhibitor).

Disorders linked to disturbances of eating behavior include bulimia nervosa and anorexia nervosa. Bulimia nervosa is characterized by compulsive overeating binges followed by inappropriate compensatory behaviors such as vomiting, fasting, excessive exercise, and misuse of diuretics or laxatives to maintain a desired weight. This eating behavior is associated with comorbid psychopathology, and can result in serious medical complications (e.g., dental erosion, esophagitis, gastrointestinal irritation, electrolyte imbalances).

The treatment of bulimia nervosa differs from the treatment of common forms of obesity. It may include cognitive-behavioral therapy, group therapy, family therapy, individual psychotherapy, and pharmacotherapy (e.g., antidepressants). Since bulimia nervosa is associated with marked alteration in monoaminergic systems (Benedetti M.S. et al.: "monamine oxidase: from physiologicology to the design and clinical application of reversible inhibitors", *Advances in drug research* (1992), **23**, 65-125), a number of monoamine oxidase inhibitors have been tried in bulimia nervosa as reported in Liebowitz M.R. et al.: "reversible and irreversible

monamine oxidase inhibitors in other psychiatric disorders", *Acta Psychiatrica Scandinavica supplementum* (1990), **360**, 29-34; Kennedy S.H. et al.: "is there a role for selective monoamine oxidase inhibitor therapy in blimia nervosa ? A placebo-controlled trial of brofaromine", *Journal of clinical psychopharmacology* (1993), 13(6), 415-22; Priest R.G. et al.: "reversible and selective inhibitors of monoamine oxidase A in mental and other disorders", *Acta Psychatrica Scandinavica* (1995), **91**, Suppl. 386, 40-43; Wittal M.C. et al.: "Boulimia nervosa: A meta-analysis of phsychosocial and pharmacological treatments", *Behaviour therapy* (1999), **30**, 117-135.

It has now been found that reversible selective inhibitors of monoamine oxidase A (MAO-A), reversible selective inhibitors of monoamine oxidase B (MAO-B) or reversible mixed inhibitors of MAO-A and MAO-B have activity in decreasing body weight of obese patients. They may act by decreasing energy intake and/or increasing energy expenditure.

Accordingly, the present invention relates to the use of reversible selective inhibitors of MAO-A, reversible selective inhibitors of MAO-B or reversible mixed inhibitors of MAO-A and MAO-B for the manufacture of drugs intended for the treatment of obesity.

The invention therefore further relates to a method of treating obesity by administering to a patient in need of such treatment a therapeutically effective amount of a reversible selective inhibitor of MAO-A, a reversible selective inhibitor of MAO-B or a reversible mixed inhibitor of MAO-A and MAO-B.

In fact, candidates for treatment may be men and women suffering from obesity or overweight.

Among reversible MAO-A inhibitors, befloxatone, moclobemide, brofaromine, phenoxathine, esuprone, befol, RS 8359 (Sankyo), T794 (Tanabe), KP 9 (Krenitsky, USA), E 2011 (Eisei), toloxatone, pirlindole, amiflamine, sercloremine and bazinaprine may be cited.

These compounds are known and their preparation are described in the art.

Among reversible selective inhibitors of MAO-B, lazabemide, milacemide, caroxazone and IFO may be cited.

Among reversible selective inhibitors of MAO-A, reversible selective inhibitors of MAO-B or reversible mixed inhibitors of MAO-A and MAO-B the following compounds may also be cited:

- compounds disclosed in patent application EP 699680, i.e. 3,3a,4,5-tetrahydro-1*H*-oxazolo[3,4-a]quinolin-1-one derivatives and particularly [3(*S*),3a(*S*)]-3-methoxymethyl-7-(4,4,4-trifluoro-3(*R*)-hydroxybutoxy)-3,3a,4,5-tetrahydro-1*H*-oxazolo[3,4-a]quinolin-1-one and [3(*S*),3a(*S*)]-3-methoxymethyl-7-[4,4,4-trifluorobutoxy]-3,3a,4,5-tetrahydro-1*H*-oxazolo[3,4-a]quinolin-1-one,

- compounds disclosed in patent application WO 96/38444, i.e. oxazolidin-2-one derivatives and particularly (*S*)-5-methoxymethyl-3-[6-(4,4,4-trifluorobutoxy)-1,2-benzisoxazol-3-yl]oxazolidin-2-one,

- compounds disclosed in patent application WO 97/13768, i.e. oxazolidin-2-one derivatives and particularly (*R*)-5-(methoxymethyl)-3-[6-(4,4,4-trifluorobutoxy)benzofuran-3-yl]oxazolidin-2-one and (*R*)-5-methoxymethyl-3-(6-cyclopropylmethoxybenzofuran-3-yl)oxazolidin-2-one.

Befloxatone or 3-[4-(4,4,4-trifluoro-3(*R*)-hydroxybutoxy)phenyl]5(*R*)-methoxymethyl-2-oxazolidinone, which is known for its antidepressive and mild anxiolytic activity is particularly prefered as reversible MAO-A inhibitor. It is a reversible monamine oxidase inhibitor with both a very high affinity for the A isoform (MAO-A) and great selectivity versus the B isoform (MAO-B), which does not affect reuptake of noradrenaline (NA), serotonine (5-HT) or dopamine (DA).

Its chemical synthesis is described in EP 424244.

As reversible MAO-B inhibitor (*S*)-5-methoxymethyl-3-[6-(4,4,4-trifluorobutoxy)-1,2-benzisoxazol-3-yl]oxazolidin-2-one is preferred.

As reversible mixed inhibitor of MAO-A and MAO-B [3(*S*),3a(*S*)]-3-methoxymethyl-7-[4,4,4-trifluorobutoxy]-3,3a,4,5-tetrahydro-1*H*-oxazolo[3,4-a]quinolin-1-one, (*R*)-5-(methoxymethyl)-3-[6-(4,4,4-trifluorobutoxy)benzofuran-3-yl]oxazolidin-2-one and (*R*)-5-methoxymethyl-3-(6-cyclopropylmethoxybenzofuran-3-yl)oxazolidin-2-one are preferred.

The active substance according to the invention can be administred to patients in a variety of pharmaceutical forms well-known in the art and particularly in the form of compositions formulated for administration by the oral, injectable, transdermal or rectal route.

For oral administration, said compositions can take the form of tablets, dragees or capsules prepared by the conventional techniques using known carriers and excipients, such as binding agents, fillers, lubricants and desintegration agents; they can also be in form of solutions, syrups or suspensions.

For administration by the injectable route, the compositions according to the invention may be in the form of injectable solutions, suspensions or emulsions containing an acceptable oily or aqueous liquid carrier.

For transdermal administration, the composition can take the form of a patch wherein the drug can be encompassed in a gel, solution, ointment or cream.

For rectal administration, the compositions may be in the form of suppositories containing the conventional bases for suppositories.

The percentage of active compound in such compositions may be varied so that a suitable dosage is obtained. The dosage administered to a particular patient is determined by the clinician according to the mode of administration, the age and weight of the patient and the patients response. Unit dosage forms may be administered in a single dose or in multiple divided doses to provide the appropriate daily dosage.

The daily dosage for example of befloxatone can range from about 2.5 to 40 mg, preferably from about 10 to 20 mg.

The following examples relating to pharmacological data and a galenic formulation illustrate the present invention.

Example 1

FEEDING BEHAVIOUR IN FASTED RATS

Male Wistar rats (Iffa-Credo) were individually housed in polycarbonate cages (48x26.5x21.5 cm) in a temperature- and humidity-controlled animal colony room (20±2°C) with a 12-hour light dark cycle (7 a.m. - 7 p.m.). At least 1 week before the experiment, every animal was often handled and administered saline by oral route in order to avoid stress. Food and water were available ad libitum, and all testing was done in the home cage. Rats were fasted for 24 hour before testing and allowed free access to water. In the morning of the test day, rats were first assigned to either a treatment or a control group then weighed and administered drug or vehicle p.o. (10.30 a.m.) and returned to their home cage. Thirty minutes later, a measured quantity of food (RMM, Harlan Ibérica) was made available to the animals. The food intake is calculated every hour until 6 hours after the drug

administration. (WO95/11894, Gehlert et al., *J. Pharmacol. Exp. Ther.* (1998), **287**, 122-127).

Grams of food consumed by the treated animals every hour was compared to food consumed by the control animals using one-way analysis of variance with a Newman-Keuls' test.

Table

Effect of befloxatone on food consumption during light period (7 a.m.-7 p.m.) in fasted rats (24 hours). Recording and access to food 11 a.m.-2 p.m.

Group		Food intake (g)		
		0 - 1 hour	0 - 2 hours	0 - 3 hours
Control (vehicle p.o.)		7.56 ± 0.33	11.0 ± 1.33	11.84 ± 1.37
Befloxatone (3 mg/kg p.o.)		5.12 ± 0.78*	7.94 ± 1.20	10.86 ± 0.94

*p< 0.05 vs control (ANOVA test)

Example 2

FEEDING BEHAVIOUR IN FED RATS

Male Wistar rats (Iffa-Credo) were individually housed into a temperature- and humidity-controlled animal room (20±2°C) with a 12-hour light dark cycle (4.30 a.m. - 4.30 p.m.). in polycarbonate special cages with transducers connected to MacLab system. This enables to record the food consumption at every moment of day (light/dark phase). A measured quantity of food (RMM, Harlan Ibérica) is placed on the cage just before dark onset.

In order to avoid any kind of stress that could have an effect on their behaviour, every rat is administered saline and put in the cage at least 1 or 2 days before the test. The food consumption is recorded, without interruption, during these

days. Once the animal is used to the cage, the test compound or vehicle are administered, by oral route.

Grams of food consumed by the animals during the first 4 hours after drug administration was compared to food consumed by the control animals over the same period of time, using one-way analysis of variance with a Newman-Keuls' test.

Table

Effect of 7 days treatment with befloxatone (10 mg/kg/day, p.o.) on food consumption during dark period (4.30 p.m. - 4.30 a.m.) in fed male Wistar rats

Days of treatment	Food intake (g)	
	Control vehicle p.o. (n=7)	**Befloxatone 10 mg/kg/day, p.o. (n=6)**
1	3.98 ± 0.63	3.03 ± 0.40
2	5.91 ± 0.85	3.31 ± 1.00
3	7.95 ± 0.68	5.32 ± 0.69*
4	7.35 ± 0.57	6.12 ± 0.50
5	8.75 ± 0.76	6.10 ± 0.59*
6	9.69 ± 0.98	6.98 ± 0.61*
7	10.1 ± 0.74	6.95 ± 0.75*

*$p < 0.05$ vs control (ANOVA test)

These results show that in the model using **fasted rats**, befloxatone (3 mg/kg p.o.) inhibits food intake by about 25% during the first hour after administration of the drug, and in the model of **fed rats** with recording of food consumption in the dark, befloxatone (10 mg/kg p.o.), once a day for 7 days, inhibits as from the third day, food intake during the first four hours after drug administration.

Exemple 3

BODY WEIGHT GAIN STUDY IN OBESE ZUCKER RATS

Befloxatone was studied in obese (fa/fa) Zucker rats, a genetic animal model of obesity.

Experimental procedure

Animals

Genetically obese Zucker (fa/fa) male rats and lean (+/?) male littermates were purchased from IFFA CREDO (France).

One week before the start of the experiment, animals were individually housed in polycarbonate cages (45 x 30 x 20 cm), with food (A04 standard diet, UAR, France) and water *ad libitum*, in a room with controlled temperature (23°C ± 1°C), in a reversed light-dark cycle (lights off at 9 h 00, on at 21 h 00) and total refresh air (12-15 times per hour). Obese and lean rats were 13 weeks old when used and weighed 380-430 g and 280-330 g respectively.

Drug

Befloxatone was suspended in an aqueous solution with 0.5 % Tween 80, and administered orally in a volume of 5 ml/kg.

Protocol

- Animals were treated p.o., once daily (at 9 h 00) for 5 weeks.

Four groups of obese (fa/fa) rats were administered vehicle or befloxatone at the doses of 1, 3 and 10 mg/kg/day.

Two groups of lean rats were administered vehicle or befloxatone (10 mg/kg/day).

- Daily food intake and body weight were recorded (at 8 h 00).

Results

Results are expressed as mean ± SEM for each treatment group. A two-way

ANOVA with repeated measures on time factor was conducted on food intake and cumulative body weight gain across weeks of befloxatone administration.

In obese rats, befloxatone induced a decrease (but non significant) of food intake over the treatment period. In lean rats this effect was more pronounced as food intake was significantly decreased on weeks 1 and 4.

A 5-week chronic treatment with befloxatone induced a dose related reduction of body weight gain in obese rats. This effect was significant from the first week of treatment for the dose of 10 mg/kg/day. In lean rats befloxatone (10mg/kg/day) also induced a similar and significant reduction of body weight gain. At the end of the treatment, weight gain was reduced by 26% ($p<0.05$) and 24% ($p<0.01$) in obese and lean rats respectively.

Example 4

ORAL FORMULATION

Befloxatone	2.5 mg	0.125 kg
Maize starch	5 mg	0.250 kg
Lactose monohydrate	83 mg	4.150 kg
Povidone K29/32	5 mg	0.250 kg
Crospovidone	4 mg	0.200 kg
Magnesium stearate	0.5 %	0.025 kg
size 3 gelatine capsule		

The befloxatone and approximately 10% of the lactose (415 g), were premixed for 10 minutes using a Turbula mixer. The mixture was then transferred to a Diosna mixer-granulator. The remainder of the lactose, the maize starch, the povidone, and half the crospovidone were added and mixed for 3 minutes. A sufficient quantity of water was added (13%) and the mixture granulated for 3 minutes. The granulate was dried in a ventilated oven and calibrated at 0.63 mm. The rest of the crospovidone, plus the magnesium stearate was added to the resulting granulate, and the whole was mixed using a Turbula mixer for 10 minutes, and then filled into size 3 capsules to a unit mass of 100 mg.

Claims

1. Use of a reversible selective inhibitor of monoamine oxidase A, reversible selective inhibitor of monoamine oxidase B or a reversible mixed inhibitor of monoamine oxidase A and B for the manufacture of drugs intended for the treatment of obesity.

2. Use of a reversible mixed inhibitor of monoamine oxidase A and B according to claim 1.

3. The use according to claim 2 wherein the reversible mixed inhibitor of monoamine oxidase A and B is chosen among [3(*S*),3a(*S*)]-3-methoxymethyl-7-[4,4,4-trifluorobutoxy]-3,3a,4,5-tetrahydro-1*H*-oxazolo[3,4-a]quinolin-1-one, (*R*)-5-(methoxymethyl)-3-[6-(4,4,4-trifluorobutoxy)benzofuran-3-yl]oxazolidin-2-one and (*R*)-5-methoxymethyl-3-(6-cyclopropylmethoxybenzofuran-3-yl)oxazolidin-2-one.

4. Use of a reversible selective inhibitor of monoamine oxidase B according to claim 1.

5. The use according to claim 4 wherein the reversible selective monoamine oxidase B is chosen among lazabemide, milacemide, caroxazone and IFO.

6. The use according to claim 4 wherein the reversible selective monoamine oxidase B is (*S*)-5-methoxymethyl-3-[6-(4,4,4-trifluorobutoxy)-1,2-benzisoxazol-3-yl]oxazolidin-2-one.

7. Use of a reversible selective inihibtor of monoamine oxidase A according to claim 1.

8. The use according to claim 7 wherein the reversible selective inhibitor of monoamine oxidase A is chosen among befloxatone, moclobemide, brofaromine, phenoxathine, esuprone, befol, RS 8359 (Sankyo), T794 (Tanabe), KP 9 (Krenitsky,

USA), E 2011 (Eisei), toloxatone, pirlindole, amiflamine, sercloremine and bazinaprine.

9. The use according to claim 7 wherein the reversible selective inhibitor of monoamine oxidase A is befloxatone.

10. The use according to claim 9 wherein the dosage amount of befloxatone is from about 2.5 to 40 mg per day.

11. The use according to claim 10 wherein the amount of befloxatone to be administered is from 10 to 20 mg.

12. The use according to any of claims 1 to 11 wherein the inhibitor of monoamine oxidase is intended for administration by the oral, injectable, transdermal or rectal route.

* C L M S *