Sleep which is often disturbed!
It affects us all.

Dear Healthcare friends,

Fascinating letters and interviews to understand the regulation of the sleep-wake system

With a passion for what I call anthropo-logic and the desire to pass on my scientific knowledge as widely as possible, I sent you **a series of letters humorously penned by the hormonal glands:** thyroid, adrenal glands, testicles, ovaries, hypophysis and epiphysis or pineal gland.

They helped you understand the **discovery** made by my colleague and friend Pr Jean-Bernard Fourtillan: the formidable sleep-wake regulation which acts naturally on all our organs, differently in the day and night. The pineal gland regulates our body by simultaneously producing the 3 hormones from Serotonin: Melatonin (MLT), 6-Methoxyharmalan (6-MH) and Valentonin (VLT).

The fictional interviews with James Parkison and Alois Alzheimer, and those in which they question Jean Bernard Fourtillan, are extremely important, as they provide you with all the information you need to understand this providential discovery of the sleep hormone and the wake hormone.

This discovery is simultaneously disseminated to the general public and scholars, while profits go to a spiritual foundation.

Jean-Bernard Fourtillan and I met while working in our respective research fields, more than forty years ago. We providentially met again recently and decided to share our complementary and mutual skills to be of service to as many people as possible.

The discovery was officially announced by Jean-Bernard Fourtillan at the National Pharmaceutical Academy on 2 December 2015.

Given the prevalence and frequency of the diseases which affect so many people, we decided to simultaneously inform the general public and health professionals, as well as chemists and experts in the production of medicinal products.

With its therapeutic applications and the new medicinal products it will generate, this discovery has enormous financial implications – costs and revenue – which pharmaceutical Laboratories are well aware of, as they are all looking for new active molecules, particularly for neurodegenerative diseases such as Alzheimer's, for which there has up until now been no effective medicine.

Aware of all these implications, Jean Bernard Fourtillan and his wife transferred the ownership of the patents guaranteeing the intellectual protection of these new medicinal products (dual-compartment

transdermal patch, containing VLT and 6-MH) to the foundation they created, the **Sister Josefa Menéndez Fund**, by way of a donation. Together, Jean-Bernard Fourtillan, Chairman, and myself as vice-Chairman, are in charge of running this **foundation**, which focuses on research and caring for patients suffering from neurological disorders.

This fund receives donations and will be paid royalties, as owner of the intellectual property rights, on the sales of medicinal products derived from the discovery. All the proceeds will go towards medical and scientific research with a view to improving the treatment of neurological disorders, as well as any other disorders caused by dysfunctions of the Sleep-Wake system. They will also support philanthropic projects relating to patients suffering from neurological disorders.

The manufacturing of the patches containing the sleep-wake regulation hormones is underway. They will be available to the patients concerned in the 3rd quarter of 2017. We wish to remain free of all industrial lobbies, which means that the foundation must advance the funds required to develop the patch manufacturing process. We are therefore counting on your help, in the form of donations of all sizes to the Sister Josefa Fund, to independently finance this production, until patent licences are granted by the Sister Josefa Fund to pharmaceutical Laboratories, who will be in charge of marketing them.

Our next interviews will relate to depression, psychoses and other therapeutic applications of the discovery, including Attention Deficit/Hyperactivity Disorders (ADHD), which can be treated with the sleep and wake hormone patches.

Is our sleep truly restorative after the hard days we all experience? Who does not, or has never had trouble sleeping? What type of sleep results from current "sleeping pill" medications?
Now it is my turn to interview the one who discovered the sleep hormone, my colleague and great friend Professor Jean-Bernard Fourtillan. Let's get right to the topic of interest to us all, young and old alike.

Question 1: What do you think of Melatonin? Is it really the sleep hormone?

NO! Melatonin is not the sleep hormone.

Melatonin is secreted by the pineal gland or epiphysis during the night, i.e. when we sleep. Tzischinsky's research into young and old insomniac subjects, published in 1994 (1), showed that the amount of melatonin excreted in urine in the form of "sulfo-conjugated" metabolites diminishes in proportion to the level of insomnia. This clearly suggests that the **secretion of Melatonin is necessary for our sleep.** We therefore had every reason to believe that Melatonin was the sleep hormone.
In the sleep studies we carried out in different animal species, Melatonin behaved like a placebo. Even though it has no hypnotic effect, its secretion remains necessary for our sleep.

Therefore Melatonin is not the sleep hormone; it is the neuro-protective hormone. During its nocturnal secretion, its powerful reducing properties help eliminate oxygenated free radicals, which destroy all the body cells, particularly the neurons. Melatonin therefore gets rid of ("cleanses") oxygenated free radicals in the nerve tissue when we sleep. Otherwise, in the absence of Melatonin, we lose neurons.

This is clearly explained in the video: **"The Sleep-Wake system in Creation"**, Pr J.B. Fourtillan (YouTube, duration: 14min 35s + 2min 13s)

To return to Tzischinsky's research, it confirms what we learn from the discovery of the hormones of the Sleep-Wake system, i.e. that the **amount of Melatonin secreted by the pineal gland is a quantitative marker of the secretion of Valentonin, the hormone actually responsible for sleep.** This hormone is produced from serotonin, during a common biochemical process of enzyme acetylations ("biochemical cascade"), which successively leads to Melatonin, 6-Methoxyharmalan and Valentonin.

Question 2: How did you discover the actual sleep hormone, Valentonin?

In the early 1990s, everybody was interested in Melatonin but nobody knew how to measure it properly, with the required sensitivity. This hormone is produced naturally by the pineal gland, and released in the bloodstream in very small doses. Plasmatic levels are very low (2), around a few picograms (3), or a few dozen picograms, per millilitre of blood plasma.

This is why the biological analysis laboratory of my CEMAF Biomedical Research Centre developed a method to measure Melatonin, – the specialists will understand – by combining gas chromatography with mass spectrometry, which we published in 1994 (4).

Thanks to this extremely sensitive measurement method, I discovered the existence of Valentonin, the sleep hormone; and subsequently, by way of logical deduction, sleep and wake regulation.

As I explained in your **letter number 142,** which everyone can read on **your website**, during my virtual interview with James Parkinson and Alois Alzheimer, I understood the regulation of the sleep-wake system one fine day in April 1994.

My intuition told me that, in the pineal gland at night, the enzyme acetylation reaction of **serotonin**, which results in the formation of **melatonin**, continued to give rise to an **N-acetylated beta-carboline**. This is a molecule from the biochemical family of beta-carbolines, as I explained in previous letters.

I became convinced that this molecule, the chemical structure of which I had just discovered, was the sleep hormone. I called it **"Valentonin".**

In the next few days, after quickly synthesising Valentonin, I managed to highlight its hypnotic properties in dogs, a nocturnal sleep animal like man. **It ensures truly restorative physiological sleep, i.e. natural sleep,** unlike the sleeping pills available on the market, such as benzodiazepines and similar drugs, which provide non-restorative anaesthetic sleep, with many adverse effects. These effects are mentioned on leaflets in such small print that nobody reads them, not even physicians!
I highlighted the presence of Valentonin in the pineal gland during sleep, in different nocturnal sleep animals (chickens, dogs, etc.).

The circumstances of my discovery of Valentonin are recounted on page 38, Pesp 4 of my book: **"The pineal gland and the Sleep-Wake system. Therapeutic applications"** (for sale on Amazon).
Ultimately, **I had to imagine the biosynthesis of Valentonin, the genuine sleep hormone, before I**

actually discovered it, as its levels in blood plasma are undetectable. Its circulating levels are even lower than those of Melatonin, and cannot be measured.

Question 3: Why did you wait more than 20 years to announce such a major discovery to the scientific community?

In 1994, I realised that this was a major discovery as this natural hormone, easy to synthesise, was the first hypnotic compound capable of producing physiological sleep. It is characterised – which can be verified on an electroencephalogram – by the abundance of deep, truly restful sleep for the entire body, and REM sleep, necessary for the memory. This is exactly what is lacking in people knocked out by current hypnotics.

The pharmacological properties of Valentonin suggested that it was an ideal candidate for a hypnotic drug, compared with available sleeping pills, benzodiazepines and related compounds (Zolpidem, Zopiclone), which provide anaesthetic, non-restorative sleep for the body, with amnesia-inducing effects (loss of memory of recent events) and numerous damaging adverse effects.

This is why I decided to file 17 invention patents in 1994, to guarantee the intellectual protection of this discovery (see references **5**-1 to **5**-17, complete list of the 17 invention patents filed for Valentonin and 569 new valentoninergics, synthetic replacement derivatives). This took a lot of time and energy!

Question 4: What are the scientific consequences of the discovery of Valentonin? What can we learn from it?

Until Valentonin was discovered in 1994 – and this is still true of researchers who have not yet heard of my discovery – **we were completely unaware of how our body works alternately in 24-hour periods, in sleep mode and in waking mode.** In short, we knew nothing about this subject!!

The identification of Valentonin was key to the discovery of the Sleep-Wake system, and the numerous resulting therapeutic applications.

Question 5: Can you tell us how you transitioned from discovering Valentonin to discovering the Sleep-Wake system?

In 2006, 12 years after I identified Valentonin, I discovered the existence of the Sleep-Wake system and its mechanism to regulate the body's psychic and vegetative life (YouTube video: **"The Sleep-Wake system in Creation"**).

As I examined the biosynthesis mechanism of Valentonin in the pineal gland, I discovered **the wake hormone: 6-Methoxyharmalan (6-MH).** Along with chemist colleagues, we identified 4 possible paths which all involve the formation of a compound, **6-Methoxyharmalan (6-MH), the chemical formula of which is identical to that of Valentonin (VLT), with one less acetyl group on the nitrogen atom of the beta-carboline skeleton.** The specialists can understand these biochemical aspects which I have to clarify.

This compound, 6-MH, formed by the acetylation of Melatonin in the biochemical cascade which leads, in 3 successive acetylation phases, from serotonin to Valentonin, **is none other than the wake hormone.**
I learned from a scientific literature review, more specifically of the Science magazine, that this compound had already been found in the pineal gland of cattle slaughtered during the night by Mc ISAAC, in 1961**(6)**, in the USA. Having formally identified 6-MH, Mc ISAAC studied its pharmacodynamic properties. The results are surprising when comparing the pharmacological profiles of the 2 sleep and wake hormones.

With 6-MH, a reversal of the pharmacodynamic properties of Valentonin is observed, which coincides with the disappearance of the acetyl group on the nitrogen atom (N) of the sleep hormone.
This is right within the area of medicinal chemistry, my favourite speciality!
Unlike Valentonin, **6-Methoxyharmalan:**
– has significant psychostimulating properties, with the same level of intensity as LSD, as explained in previous interviews. This helps keep the body in waking mode during the activity period;
– increases blood pressure and **heart rate;**
– and also **causes** muscle contraction.
6-Methoxyharmalan, the wake hormone, can be characterised as the daytime and cognition hormone.

Question 6: What is the Sleep-Wake system? How does it work?

It consists of 3 hormones, Melatonin (MLT), 6-Methoxyharmalan (6-MH) and Valentonin (VLT). They are simultaneously secreted by the pineal gland, for 8 hours, when we sleep. **They are biosynthesised in the pineal gland via 3 successive chemical reactions, called enzyme "acetylations", based on serotonin, within the same biochemical cascade.**

The key role of MLT is to protect the neurons, thanks to its reducing properties, against oxidative attack which destroys the oxygenated free radicals accumulated throughout a working day. At the end of the secretion, when waking in the morning, the brain's nerve tissue is cleansed, and the body is ready to face another day.

Sleep and wake regulation is described in the book and the brochure: **"The pineal gland and the Sleep-Wake system. Therapeutic applications"**, which I published (for sale on Amazon). In **letter no. 142**, published in November, I explained how the 2 pineal hormones, VLT and 6-MH, act.

They modulate the responses of the specific neurotransmitter receptors, located on synapses, junction points between neurons, and of the hormone receptors located on all endocrine glands: hypophysis, adrenal glands, ovaries, testicles, thyroid, in rest mode at night and active during the day. They amplify or reduce, depending on whether the body is in wake or sleep mode, the responses of these receptors, throughout the body.

It is surprising and extraordinary that these two small molecules alone, 6-MH and VLT, are capable of completely controlling how the body works, by putting it in wake and sleep mode alternately for 24 hours. This is what sleeping pills do not and cannot do.
Please read these letters again on the **website** to fully understand all this.

Question 7: How do you explain that these 2 hormones, with opposite actions, notably in terms of vigilance, are capable of putting us to sleep at night and keeping us awake during the day, when they are secreted simultaneously while we sleep?

This can be explained by their differing pharmacokinetic properties. Firstly, VLT is eliminated far more quickly than 6-MH and secondly the amount of VLT secreted by the pineal gland during the night is approximately 4 times higher than that of 6-MH.

As a result, during the nocturnal secretion period of the two hormones, the body is in sleep mode as the VLT concentration in the body is higher than that of 6-MH. The opposite happens during the day, as soon as hormone secretions stop, due to the rapid elimination of VLT.

A marvel of biochemical activity!

It should be pointed out that the amounts of the 2 hormones secreted by the pineal gland, albeit very low (a few dozen microgrammes are secreted for approximately 8 hours), are extremely effective.

Question 8: Valentonin, which ensures our sound sleep under physiological conditions, is the ideal candidate for developing a hypnotic drug as natural as possible. You ultimately selected this natural hormone to treat sleep disorders. But why did you synthesise 569 VLT surrogate molecules, from 1994 to 2007, which you called "Valentoninergics", described and protected in 16 patents?

Valentonin cannot be taken orally, as it is entirely destroyed in the acidic environment of the stomach. In 1994, at such an early stage of the discovery, this was a major inconvenience for me, as its intravenous injection all year round to get people to sleep was unthinkable.

The VLT molecule can be rendered stable in an acidic environment by chemically modifying it, and therefore synthesising surrogates which can be taken orally.

The pharmacological properties (pharmacodynamic and pharmacokinetic activities) and modes of action of these three hormones are closely correlated with their chemical structures. The structure-activity relationships of VLT and 6-MH are described in the YouTube video entitled: **"The Sleep-Wake system in Creation"**. Take the time to watch it and listen.

The detailed identification of the chemical structure elements responsible for the hypnotic activity of VLT (pharmacophore support) led me to synthesise 569 new VLT surrogate hypnotic molecules, which are all stable in an acidic environment and can therefore be taken orally.

Question 9: Why, since you synthesised 569 hypnotic molecules which can be taken orally and all of which, without exception, provide restful physiological

sleep for the body, did you eventually choose Valentonin, which you opted to administer transdermally in the form of a patch, combined with 6-MH?

In the end I had no other choice than to select VLT, the natural hormone, to treat sleep disorders and all other neurological disorders due to the deficient hormone secretions of the pineal gland, which we have now identified: nervous breakdowns, Parkinson's and Alzheimer's neurodegenerative diseases, during which patients obviously always suffer from sleep disorders.

Here is why:
1- Given their "cascade" biosynthesis, the 3 pineal hormones are always secreted by the pineal gland in the same proportions. This means that any quantitative variation, in deficit or in excess, of the endocrine hormonal function of the pineal gland, will impact all 3 hormones in the same way.
In this context, **the deficient secretion of VLT, the sleep hormone, by the pineal gland, during the nocturnal rest, responsible for lack of sleep, is systematically accompanied by a deficient secretion of 6-MH, the wake hormone.**

Therefore people who have trouble sleeping during the night have vigilance, and therefore energy problems during the day. They are tired during the activity period and end up suffering from depression and anxiety. All those who have trouble sleeping acknowledge this.

2- One, the sleep hormone, does not go without the other, the wake hormone. 6-MH and VLT are the day and night hormones which control, via their opposite actions during rest and activity phases, the functioning of many organs of our psychic (thoughts and dreams) and vegetative life (respiratory, cardiac, intestinal functioning, etc.).

To restore the harmonious functioning of the body, in case of deficient hormone secretions of the pineal gland, replacement therapy must be implemented to offset this insufficiency, by simultaneously administering the 2 hormones and replicating the conditions of their physiological secretions.

They must therefore be administered during the pineal secretion period, i.e. for approximately 8 hours; and they must be released in the bloodstream at a constant rate.

There are 2 possible routes of administration:
– by intravenous infusion, for 8 hours, of a solute containing the 2 hormones, during the night. This is of course unthinkable for daily use.
– or a **transdermal administration, using dual-compartment patches, separately containing the 2 hormones, applied in the evening at bedtime and removed when waking in the morning.** We naturally opted for this solution, which we intend to apply extensively to the many people who need it.
3- **The oral route is not viable,** as it is incapable of reproducing the physiological secretion curves. In addition, **only the pharmacokinetic characteristics of VLT (particularly its elimination rate) make it possible to combine VLT with 6-MH, so that the prevalence time of 6-MH (time when the concentration of 6-MH in the body becomes higher than that of VLT) is respected, as soon as the patch is removed when waking in the morning.**
This is why it was impossible to use one of the 579 valentoninergic compounds that we synthesised, the chemical structures of which differ from natural hormones, as their pharmacokinetic properties were ill

suited to 6-MH to achieve this prevalence objective.

The treatment of sleep disorders, which will be available to patients in the summer of 2017, will consist of applying a dual-compartment transdermal patch (currently in production) at bedtime, releasing 50 microgrammes of 6-Methoxyharmalan and 200 microgrammes of Valentonin over approximately 8 hours. The patch will be removed when waking in the morning.

Question 10: Why are currently available sleeping pills, benzodiazepines and related drugs, ineffective and even dangerous?

For the moment, sleeping pills available in pharmacies, benzodiazepines and related drugs (Zolpidem, Zopiclone), are ineffective and even dangerous medicinal products.

They cause "anaesthetic", non-restorative sleep for the body sleep and, in addition to their amnesia-inducing effects, they cause the anterograde amnesia phenomenon, i.e. the loss of memory of recent events.

In other words, they aggravate, and can even initiate, the Alzheimer and/or Parkinson processes based on the most fragile cerebral zone. We know that, when used regularly, they increase the risk of developing these diseases by 50%!

In addition, these "hypnotic" sleeping pills fail to live up to their name as their adverse effects are what prevails in patients, first and foremost significant insomnia and anxiety, referred to as paradoxical as they are the opposite to the desired effects for which they are taken. This is because they destroy physiological sleep.

The discovery of the Sleep-Wake system helps explain these **paradoxical anti-sleep effects of benzodiazepines and related drugs.** Their chemical structures feature the pharmacophore model (see reference 7) of 6-MH (which is also found in the chemical structure of LSD), to which they owe their psychostimulant and anxiety-inducing effects. This is why they inhibit physiological sleep, because of their antagonistic action on the 5-HT2C serotoninergic receptors, an action identical to that of 6-methoxyharmalan, the wake hormone, which explains the frequent occurrence of insomnia as the number one adverse effect.

By the same mechanism, they maintain and promote nervous breakdowns.

As they possess the other pharmacological properties of 6-MH, they influence the hormone secretions of endocrine glands, notably by increasing the secretion of prolactin; they cause hyperprolactinaemia (as its name suggests, prolactin is the lactation hormone), responsible for clear or slightly opalescent nipple discharge, known as "galactorrhoea" in women, and minor glandular swelling behind the nipple in men, known as "gynaecomastia". Progression to breast cancer in women, and even in men, are well documented and less and less infrequent.

These ineffective medicinal products, harmful to human health, should be prohibited in the treatment of sleep disorders and nervous breakdowns and exclusively reserved to anaesthesiology.

Question 11: As a hypnotic medicinal product, what will be the benefits of dual-compartment patches of Valentonin and 6-Methoxyharmalan compared with sleeping pills?

Unlike benzodiazepines and related drugs, VLT provides you with physiological sleep characterised, on an electroencephalogram, by an abundance of deep, restful sleep and REM sleep necessary for the memory.

All this is explained in the video: **"Sleep disorders and how to treat them",** Pr J.B. Fourtillan and Pr H. Joyeux (YouTube: duration 16 min 25)

As I have just explained, **the administration of VLT alone would be insufficient to offset the deficient secretion of 6-MH and to correct the insufficient presence of the wake hormone in the body during the day.**

The dual-compartment patches, which will separately contain VLT and 6-MH, will release the 2 natural hormones in the bloodstream, by skin absorption, under conditions strictly identical, in terms of rate and quantity, to physiological secretions, during the secretion period of the deficient pineal gland at night.

This is a natural hormone replacement therapy designed to make up for the deficient secretions of the pineal gland at night.
It is administered during the secretion period, i.e. when we sleep.

The doses absorbed for 8 hours, 50 microgrammes of 6-methoxyharmalan and 200 microgrammes of Valentonin, correspond with the physiological secretions.
This treatment guarantees the absence of adverse effects.

Question 12: Is there another possible treatment for sleep disorders?

In light of the specific roles of Valentonin and 6-MH in the functioning of the body, **it would be reasonable to expect that no other sleep disorder treatment is appropriate.**

Many thanks to Jean-Bernard for these enlightening clarifications, which complement the explanations given to James Parkinson and Alois Alzheimer in previous letters.

The numerous emails received on this topic attest to the tremendous interest generated by the dissemination of this discovery. The rising, even alarming number of people who discover the first signs of Parkinson's and/or Alzheimer's disease or claim to suffer from sleep disorders at an increasingly early stage in our disorientated society, have encouraged us to let you know about the incredibly positive consequences of this discovery.

Do not hesitate to broadly circulate the information to those around you. All retirement homes

should know. Treatments are coming, so help us publicise them before we can make them widely available to the general public.

I wish you all the best for this week leading up to Christmas, the joyful celebration of an incredible birth which I will talk to you about soon.

Pr Henri Joyeux

Post-scriptum

On the **Fonds-sœur-josefa.org** website to which my wife and I entrusted all patents filed:
– **Book and Brochure** "**The pineal gland and the Sleep-Wake system. Therapeutic applications**"
– **YouTube videos**:
"**The pineal gland and the Sleep-Wake system. Therapeutic applications**", Pr J.B. Fourtillan (YouTube: duration 37 minutes)
"**Pr JB Fourtillan answers Pr H Joyeux's questions**" Pr J.B. Fourtillan and Pr H. Joyeux (YouTube: duration 1 hour)
"**The Sleep-Wake system in Creation**", Pr J.B. Fourtillan (YouTube, duration: 14min 35s + 2min 13s)
***Les causes et le traitement de la maladie d'Alzheimer enfin découverts !* (The causes and treatment of Alzheimer's disease finally discovered),** Pr J.B. Fourtillan and Pr H. Joyeux (YouTube: duration 13min 30)
***Les véritables Causes et le Traitement de la maladie de Parkinson* (The real causes and treatment of Parkinson's disease)**, Pr J.B. Fourtillan and Pr H. Joyeux (YouTube: duration 14 min 25)
"Sleep disorders and how to treat them", Pr J.B. Fourtillan and Pr H. Joyeux (YouTube: duration 16 min 25)
– **Donations** can be made to help the Josefa Fund finance, independently of the pharmaceutical industry, the development and manufacturing of patches until the TUA (Temporary Use Authorisation) is granted, which is scheduled for the summer of 2017.

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(2) Fourtillan, J.B., Brisson, A.M., Gobin, P., Fourtillan, M., Ingrand, I., Decourt, J.Ph. & Girault,
J. Melatonin secretion occurs at a constant rate in both young and older men and women.
Am. J. Physiol. Endocrinol. Metab., 280, E11-E22 (2001)
(3) 1 picogram per ml of plasma (pg/ml) is equal to 1 billionth of milligram per ml of plasma.
(4) Fourtillan, J.B., Gobin, P., Faye, B. & Girault, J. A highly sensitive assay of melatonin at the femtogram level in human plasma by gas chromatography / negative ion chemical ionization mass spectrometry. Biol. Mass Spectrom., 23, 499-509 (1994).
(5) List of 17 invention patents filed for Valentonin and 569 new valentonergics, synthetic replacement derivatives:

5-1-NOVEL MELATONIN AGONIST β-CARBOLINE DERIVATIVES AND ANALOGS WITH A

NAPHTALENIC STRUCTURE, METHOD FOR THEIR PREPARATION AND THEIR USE AS DRUGS
International application number PCT/FR95/01179, WO 96/08490 A1
Date of international publication: 21/03/1996
Priority filing date: 14/09/1994
Inventors: FOURTILLAN Jean-Bernard, FOURTILLAN Marianne, JACQUESY Jean-Claude, JOUANNETAUD Marie Paule, VIOLEAU Bruno, KARAM Omar

5-2-NEW MELATONIN AGONIST DERIVATIVES OF 3,4- DIHYDRO BETA-CARBOLINE, PROCESS FOR THEIR PREPARATION AND APPLICATION AS A MEDICINAL PRODUCT
Publication no. FR 2 724 384 – A1
National registration no.: 94 10964
Filing date: 14/09/1994
Inventors: FOURTILLAN Jean-Bernard, FOURTILLAN Marianne, JACQUESY Jean-Claude, JOUANNETAUD Marie Paule, and VIOLEAU Bruno

5-3-NEW ACYL DERIVATIVES OF MELATONIN AND MELATONINERGIC ANALOGUES, PROCESS FOR THEIR PREPARATION AND USE AS A MEDICINAL PRODUCT.
Publication no. FR 2 737 725 – A1, EP 0 851 855 B1, WO 97/06140, US 6, 004, 991, US 6, 140, 372
National registration no.: 95 09611
Filing date: 08/08/1995
Inventors: FOURTILLAN Jean-Bernard, FOURTILLAN Marianne, JACQUESY Jean-Claude, JOUANNETAUD Marie Paule, VIOLEAU Bruno, KARAM Omar

5-4- MELATONIN AGONIST DERIVATIVES OF BETA-CARBOLINE, PROCESSES FOR THEIR PREPARATION AND USE AS A MEDICINAL PRODUCT.
Publication no. EP 0 781 281B1, PCT/FR95/01179, WO 99/08490
National registration no.: 94 10964
Filing date: 14.09.1995
Inventors: FOURTILLAN Jean-Bernard, FOURTILLAN Marianne, JACQUESY Jean-Claude, JOUANNETAUD Marie Paule, VIOLEAU Bruno, KARAM Omar

5-5-HYPNOTIC BETA-CARBOLINE DERIVATIVES, PROCESS FOR THEIR PREPARATION AND THEIR USE AS MEDICINAL PRODUCTS
International Publication no. PCT/IB99/00494, WO 99/47521, US 6, 048, 868
Priority filing date: 17/03/1998
Inventors: FOURTILLAN Jean-Bernard, FOURTILLAN Marianne, JACQUESY Jean-Claude, JOUANNETAUD Marie Paule, VIOLEAU Bruno, KARAM Omar.

5-6-HYPNOTIC BETA-CARBOLINE DERIVATIVES, PROCESS FOR THEIR PREPARATION AND THEIR USE AS MEDICINAL PRODUCTS
Publication no. EP 1 064 284 B1, PCT/IB99/00494, WO 99/47521
National registration no.: 94 10964
Filing date: 17.03.1999
Inventors: FOURTILLAN Jean-Bernard, FOURTILLAN Marianne, JACQUESY Jean-Claude, JOUANNETAUD Marie Paule, VIOLEAU Bruno, KARAM Omar

5-7-NEW DIHYDROIMIDAZO [5,1-A]-BETA-CARBOLINE DERIVATIVES, PROCESS FOR THEIR PREPARATION AND APPLICATION AS MEDICINAL PRODUCTS
Publication no. FR 2 824 829 – A1
National registration no.: 01 06444
Filing date: 16/05/2001
Inventors: FOURTILLAN Jean-Bernard, FOURTILLAN Marianne, KARAM Omar, ZUNINO Fabien, JACQUESY Jean-Claude, TAFANI Jean-Pierre

5-8-DIHYDROIMIDAZO [5,1-A] -BETA-CARBOLINE DERIVATIVES, PROCESS FOR THEIR PREPARATION AND APPLICATION AS A MEDICINAL PRODUCT
Publication no. EP 1 390 367 B1, PCT/FR2002/001653, WO 2002/092598 A1, US 2006/0089372 A1
Filing date: 16.05.2002
Inventors: FOURTILLAN Jean-Bernard, FOURTILLAN Marianne, KARAM Omar, ZUNINO Fabien, JACQUESY Jean-Claude, TAFANI Jean-Pierre

5-9-COMBINATION OF A 5-HT2 RECEPTOR ANTAGONIST WITH A 5-HT2 RECEPTOR ACTIVATOR BY ALLOSTERIC MODULATION AND THEIR USE AS MEDICINAL PRODUCTS.
Publication no.: FR 2 898 358-A1; National registration no.: PCT/FR06/01444; International publication no.: WO 2007/101863
National registration no.: 06 02057
Filing date: 08/03/2006
Inventors: FOURTILLAN Jean-Bernard and FOURTILLAN Marianne

5-10-PYRIMIDINO [1',6': 1,2] PYRIDO [3,4-B] INDOLE DERIVATIVES AND THEIR THERAPEUTIC USE.
Publication no.: FR 2 901 795, PCT N° WO 2007/138081 A1; National registration no.: 06 04795
Filing date: 30/05/2006
Inventors: FOURTILLAN Jean-Bernard and FOURTILLAN Marianne

5-11-3H, 11H-OXAZOLO [3',4': 1,2] PYRIDO [3,4-B] INDOLE DERIVATIVES AND THEIR THERAPEUTIC USE.
Publication no.: FR 2908 767, PCT N° WO 2007/147819 A1
National registration no.: 06 05421
Filing date: 19/06/2006
Inventors: FOURTILLAN Jean-Bernard and FOURTILLAN Marianne

5-12-3H, 11H-OXAZOLO [3',4': 1,2] PYRIDO [3,4-b] INDOLE DERIVATIVES AND THEIR THERAPEUTIC USE.
Publication no.: FR 2908 768
National registration no.: 06 05697
Filing date: 19/06/2006
Inventors: FOURTILLAN Jean-Bernard and FOURTILLAN Marianne

5-13-1-METHYLIDENE-PYRIDO [3,4-B] INDOLE DERIVATIVES AND THEIR THERAPEUTIC USE.
Publication no.: FR 2 904 973
National registration no.: 06 07381
Filing date: 18/08/2006

Inventors: FOURTILLAN Jean-Bernard and FOURTILLAN Marianne

5-14-IMIDAZO [1',5': 1,6] PYRIDO [3,4-B] INDOLE DERIVATIVES AND THEIR THERAPEUTIC USE.
Publication no.: FR 2 912 405, PCT N° WO 2008/101824 A1
National registration no.: 07 53138
Filing date: 08/02/2007
Inventors: FOURTILLAN Jean-Bernard and FOURTILLAN Marianne

5-15-4,5,11,11A-TETRAHYDRO-1H,6H-OXAZOLO[3',4': 1,6] PYRIDO[3,4-13] INDOL 3-ONE DERIVATIVES AND THEIR THERAPEUTIC USE.
Publication no.: FR 2 914 924
National registration no.: 07 54466
Filing date: 13/04/2007
Inventors: FOURTILLAN Jean-Bernard and FOURTILLAN Marianne

5-16-NEW 1,2,3,4,6,7,12,12A-OCTAHYDRO PYRAZINO [1',2': 1,6] PYRIDO [3,4-13] INDOLE DERIVATIVES, THEIR PREPARATION AND THERAPEUTIC USE.
Publication no.: FR 2 916 200
National registration no.: 07 55137
Filing date: 18/05/2007
Inventors: FOURTILLAN Jean-Bernard and FOURTILLAN Marianne

5-17-TRANSDERMAL THERAPEUTIC SYSTEM CONTAINING VALENTONIN AND ITS USE AS A MEDICINAL PRODUCT
– Priority application:
Filing number: EP 15305161.0
Applicants and inventors: FOURTILLAN Jean-Bernard and FOURTILLAN Marianne
Filing date: 04 February 2015
– International application:
International registration number: PCT/EP2016/052376
Applicants and inventors: FOURTILLAN Jean-Bernard and FOURTILLAN Marianne
International filing date: 04 February 2016
Date of international publication: 11 August 2016
International publication number: WO 2016/124688 A1

(6) Mc Isaac, W.M., Khairallah, P.A. & Page, I.H. 10-Methoxyharmalan, a potent serotonin antagonist which affects conditioned behavior. Science, 134, 674-675 (1961).
(7) A pharmacophore consists of the pharmacologically active part of a molecule. Pharmacophores are therefore sets of active atoms which support the pharmacological activity.