The International application relates to at least one vasodilating agent, such as glyceryl trinitrate, for acute prevention or treatment of patients suffering from somnolepsy, a new sleep disorder characterized by somnoleptic seizures and/or sleep attacks, and acute treatment of sleep attacks in other known sleep disorders. The vasodilating agent has an onset of action within 15 to 60 seconds after administration and may thus prevent sleep attacks when a forewarning of a sleep attack is experienced. The effect of the vasodilating agent may be prolonged by further administration of an immediate release formulation comprising a CNS-stimulant, such as methylphenidate.
VASODILATING AGENTS FOR THE TREATMENT OF SLEEP ATTACKS

Technical field of the invention

The present invention relates to at least one vasodilating agent for acute prevention or treatment of patients suffering from somnolepsy, a new sleep disorder characterized by somnoleptic seizures and/or sleep attacks, and acute treatment of sleep attacks in other known sleep disorders.

Background of the invention

Sleep is a normal state of decreased consciousness and lowered metabolism during which the body rests. As a natural, necessary, and daily experience, sleep consists of REM (rapid eye movement) sleep and has four stages of non REM sleep, through which we cycle several times a night. A sleep disorder is any condition that interferes with our regular sleep cycle, ranging from insomnia to narcolepsy.

Sleep is something everyone experiences every day and the average person sleeps approximately one third of his or her lifetime. We all recognize that sleep is a necessity and that although we can go without it for a while, it eventually becomes as important to our health and well-being as food, air and water. We also know that when we sleep well, we seem to wake refreshed and alert, and generally feel ready to face the day. When we do not sleep well, we will feel grumpy and everything may be a little bit more difficult to do. People who regularly experience problems falling asleep or staying asleep may be suffering from some form of sleep disorder. Serious sleep disorders can wreck out personal lives, make us unproductive at work, injure the quality of our lives and overall make a person dangerous to himself or others when for example working with machines or driving a motor vehicle.

Although sleep is something common to us all, many people suffer from some kind of sleep disorder. Some sorts of sleep disorders involve poor ability of falling asleep and/or staying asleep at night, insomnia may be an example of this, and like other sorts of sleep disorders involve daytime sleepiness and sleep attacks.
Sleep disorders which may lead to daytime sleep attacks may not only be a problem for the person suffering from it, but it may lead to life-threatening incidents, such as work related accidents or driving accidents. In addition, the sleep disorders with daytime sleep attacks may cause damage to not only the person suffering from it but to other people as well, if the state of daytime sleepiness is severe and experienced while the person is moving in public places, such as when driving a car.

In several types of sleep disorders daytime sleepiness is an ordinary symptom. In some cases the daytime sleepiness is associated with a large increase in total daily amount of sleep without any genuine feeling of restoration. In other cases, sleepiness can be alleviated temporarily by naps but reoccurs shortly thereafter and can result in sleep attacks.

Several types of sleep disorders with more or less daytime sleepiness and sleep attacks are known, such as sleep apnoea, insomnia, narcolepsy, idiopathic hypersomnia, restless legs and periodic leg movements.

Narcolepsy and idiopathic hypersomnia and sleep apnoea are sleep disorders where the patients suffer from severe daytime sleep attacks.

**Narcolepsy**

Narcolepsy is a sleep disorder which is characterised by cataplexy, sleep fragmentation and symptoms of abnormal REM sleep. Narcolepsy is also associated with disturbance in attention and concentration, and frequently with fatigue and depression.

Narcolepsy may be with and without cataplexy, which is a sudden attack of muscle weakness, and is therefore called either narcolepsy with cataplexy or narcolepsy without cataplexy.

Individuals suffering from narcolepsy also have excessive daytime sleepiness (EDS) which is characterized by episodes of sleep attacks or lapses into sleep across the daytime. These naps are refreshing in nature. Patients sleep for a short
duration and awaken refreshed. The pattern may repeat itself through the day with varying frequencies. Sleepiness is more likely to occur in boring monotonous situations that require no active participation, for example watching television, but these sleep attacks may also occur in special situations such as eating, walking or driving a car. These sleep attacks cannot be prevented without medical treatment.

Two of the following symptoms: Cataplexy, sleep paralysis, hypnagogic- and hypnopompic hallucinations must be present besides two or more sleep onset REM periods in a multiple sleep latency test (MSLT). This test is described in detail later. Nocturnal sleep disruption commonly with frequent awakenings may be experienced for individuals with narcolepsy, with and without cataplexy and excessive daytime sleepiness and sleep attacks are usually present. These and other sleep related terms are described in detail later.

Narcoleptic patients may report memory lapses and may show inappropriate activity and poor adjustment to abrupt environmental demands.

Patients with narcolepsy typically have nocturnal sleep disruption where frequent awakenings may occur. Nocturnal sleep disruption occurs in approximately 50% of narcoleptics and can even be the presenting symptom. However, patients with narcolepsy typically have a normal length of night sleep.

REM sleep disorder is a diagnostic criteria for patients having narcolepsy.

An all night polysomnography can demonstrate an increase in the amount of stage 1 sleep, and there may be a disruption of the normal sleep pattern, with frequent awakenings. By following an all-night polysomnography, a multiple sleep latency test (MSLT) shows a mean latency of less than eight minutes, and two or more SOREMP's (sleep onset rapid eye movement periods). The mean sleep latencies in narcoleptic patients have been shown to be $3.1 \pm 2.9$ minutes. The terms "MSLT" and "SOREMP's" are described in detail later.

Individuals with narcolepsy without cataplexy may, however, experience cataplexy-like episodes such as muscle weakness, triggered by unusual emotions such as stress, sex, or intense activity/exercise.
**Idiopathic hypersomnia**

Idiopathic hypersomnia is characterized by a constant and severe excessive daytime sleepiness with prolonged but unrefreshing naps or sleep attacks of up to three or four hours, and great difficulty waking up either in the morning or at the end of a nap.

Individuals diagnosed as having idiopathic hypersomnia commonly have symptoms of sleep drunkenness. The individuals typically do not awaken to alarm clocks and frequently use special devices or procedures to wake up. Furthermore, individuals with idiopathic hypersomnia have complaint of severe excessive daytime sleepiness which results in prolonged unrefreshing sleep attacks.

Polysomnographic tests show that individuals having idiopathic hypersomnia have a normal nocturnal sleep pattern, including a normal REM-sleep. However, MSLT is decreased to a mean value of 6.2 ± 3.0 minutes.

Cataplexy is not observed for individuals having idiopathic hypersomnia.

Associated symptoms may be headaches, which may be migrainous in character, orthostatic hypotension and peripheral vascular complains such as cold hands and feet.

Idiopathic hypersomnia may be with or without long sleep time. For idiopathic hypersomnia with a long sleep period, the major sleep episode is prolonged to at least 10 hours, typically 12 to 14 hours, with few or no awakenings. Post-awakening confusion (sleep drunkenness) is often reported. In a research setting, idiopathic hypersomnia with long sleep time is typically diagnosed only in the presence of long sleep time and is a unique disease entity. A polysomnographic monitoring demonstrates sleep of prolonged duration, with no abnormality in rapid eye movement (REM), and short sleep latency.

Individuals characterized by having idiopathic hypersomnia without a long sleep time have either a normal or slightly prolonged (less than 10 hours) night sleep, usually with few or no awakenings.
Individuals suffering from idiopathic hypersomnia may have daytime naps or sleep attacks which are several hours long, but they are not refreshing. No matter how much sleep they get, they are still sleepy.

Some individuals with idiopathic hypersomnia have symptoms that resemble narcolepsy. Examples are sleep paralysis and hallucinations. But people with idiopathic hypersomnia do not have the symptom of cataplexy. They also do not have as many episodes of quickly entering REM sleep as someone with narcolepsy.

**Restless legs**

Restless legs is a condition correlated to a nearly irresistible urge to move the legs during rest (sitting or lying). The condition often disturbs the patients’ ability to go to sleep and their night sleep, leading to excessive daytime sleepiness (EDS) and sleep attacks during day time.

**Sleep apnoea**

Sleep apnoea is a condition characterized by repetitive episodes of complete apnoea or hypopnoea occurring during sleep leading to low oxygen saturation. Often more than 100 episodes during a night sleep, resulting in many awakenings and no or little sleep in slow wave sleep stages. The patients suffer from EDS and sleep attacks during day time.

**Periodic leg movements**

Periodic leg movements is a condition characterized by periodic episodes of repetitive limbs movements during sleep and by clinical sleep disturbance that cannot be accounted for by another primary sleep disorder, resulting in EDS and sleep attacks during day time.

**Insomnia**

Insomnia is defined as a complaint of difficulty initiating sleep, maintaining sleep, or waking up too early or sleep that is chronically nonrestorative or poor in quality. The condition leads to daytime sleepiness and sleep attacks.
ADHD and ADD
The two disorders are mostly present in children and young adults. The disorders are characterized by attention deficits and in some of the individuals also by episodes of hyperactivity during the day. The individuals suffer from restless night sleep leading to daytime attention deficits/sleep attacks. The MSLTs reveal an abnormal short sleep latency.

Methylphenidate
Methylphenidate is a drug which is well known in art. The following documents describe immediate- sustained- or controlled release formulations comprising methylphenidate and/or the use thereof as prophylactic treatment. These formulations cannot be used for acute treatment of sleep attacks as the onset of action is not fast enough. The immediate release formulation has an onset of action after 15 minutes.

WO 97/03 673 describes a sustained release formulation of methylphenidate used for treatment of e.g. narcolepsy or hypersomnia.

US 7,083,808 describes an oral controlled/modified release methylphenidate formulation. Furthermore, the document describes multilayered preparations with both a sustained release layer and an immediate release layer, and it is described that the onset of action of methylphenidate occurs from about 0.5 to about 4 hours after the oral dosage form has been administered.

Furthermore, the document describes that the oral dosage form comprises an effective amount of methylphenidate and a modifying material which causes the formulation to provide an in vitro dissolution of the drug of from about 0 to about 45% released after 15 minutes, from about 10 to about 50% released after 1 hour, from about 30 to about 80% released after 4 hours, and at least 65% released after 8 hours.

WO 05/120 468 describes a multilayered controlled release methylphenidate pellet.
WO 04/091 546 describes treatment of attention deficit disorder (ADD), attention deficit hyperactive disorder (ADHD) and narcolepsy by administering a CNS-stimulant and an opioid antagonist in either immediate release tablets or sustained release tablets. The opioid antagonist is administrated to prevent abuse of methylphenidate. The immediate release tablets release methylphenidate over a 1 hour interval after administration.

WO 99/03 458 describes that methylphenidate is used prophylactically for controlling sleep attacks and accompanying tensions caused by narcolepsy.

WO 99/03471 describes dosage forms for oral administration of methylphenidate for treatment of ADHD, where the dosage forms provide a substantially immediate dose of methylphenidate upon digestion, followed by one or more additional doses having a predetermined sustained release form.

The inventor of the present invention has found a group of individuals having a new sleep disorder which cannot be categorised as any of the hitherto known types of sleep disorders. This new sleep disorder is called “Somnolepsy”. There is a need for a medication to acute treatment of this group of individuals having the symptoms of the new disease of which somnoleptic seizures and sleep attacks are the most prominent. Further there is a need for a medication for acute treatment of sleep attacks in other sleep disorders.

**Summary of the invention** The present invention provides at least one vasodilating agent for acute prevention or treatment of somnoleptic seizures and/or sleep attacks. Preferably, the onset of effect of the vasodilating agent is within 15 seconds to 1 minute after administration, such as within 30 seconds after administration. In particular, the present invention relates to administration of at least one vasodilating agent, such as glyceryl trinitrate, and at least one CNS-stimulant, such as methylphenidate, wherein said administration provides a fast acting and long lasting effect.

In one aspect, the present invention relates to a method of preventing or treating somnolepsy, somnoleptic seizures and/or sleep attacks, said method comprises
administering to an individual in need thereof a fast acting composition comprising an effective amount of at least one vasodilating agent. Further, the vasodilating agent may be administered in combination with an effective amount of at least one CNS-stimulant.

5 In another aspect, the present invention relates to at least one vasodilating agent for acute prevention and/or treatment of somnoleptic seizures and/or sleep attacks.

10 In still another aspect, the present invention relates to a composition comprising at least one acute vasodilating agent in combination with at least one CNS-stimulant.

**Detailed description of the invention**

15 All patent and non-patent references cited in the present application, are hereby incorporated by reference in their entirety.

Furthermore, it must be noted that as used in the present application, the singular forms "a" and "the" include plural referents unless the context clearly dictates otherwise. For example, reference to "a composition" includes a plurality of such compositions.

One aspect of the present invention is at least one vasodilating agent, e.g. glyceryl trinitrate in a fast release and fast acting composition for use in prevention and/or treatment of somnoleptic seizures or sleeps attacks in disorders, in which the individual suffer from sleep attacks.

The inventor of the present invention has identified a new type of sleep disorder with symptoms which differ from the previously known sleep disorders, such as for example sleep apnoea, idiopathic hypersomnia or narcolepsy. In the context of the present invention this new sleep disorder is called "somnolepsy". As the symptoms, of which somnoleptic seizures/sleep attacks are the most prominent, similar to sleep attacks in other sleep disorders, there is a need for a composition
for acute treatment, with an onset of action within 30 to 60 seconds after administration, of these somnoleptic seizures and/or sleep attacks.

As described herein the term "sleep disorder" generally relates to conditions where individuals or patients have difficulty in falling asleep and/or staying asleep, or experience unrefreshing sleep and sleep deprivation. Further, the term "sleep disorder" relates to conditions where individuals suffer from abnormalities in their sleep pattern during the night and abnormal sleep events during daytime. Somnoleptic seizures and sleep attacks relate to a condition, in different to other sleep orders, in which the individuals are overwhelmed by an undesirable need to sleep.

The term "individual" as used herein, refers to both humans and animals.

In the following, somnolepsy and the symptoms that characterise this sleep disorder are described.

**Somnolepsy** is characterized by somnoleptic seizures, just as epilepsy is characterized by epileptic seizures appearing in a person during the day.

A somnoleptic seizure is a condition where the individual goes through a gradual transition from being awake, passing through a feeling of absence or not being present with fleeting loss of consciousness to merge into a short refreshing sleep. However, some individuals can be interrupted from the state of absence and loss of consciousness and will not fall a sleep.

The frequency of these seizures varies considerably among individuals. For some, there are only hours or less between the seizures, whereas for others there may be days between the seizures. Most often patients suffer from one or two seizures a day. The duration of a somnoleptic seizure is short, typically from 30 seconds to 30 minutes, most often 1-5 minutes. As mentioned earlier some individuals may merge into sleep, and if so the individuals often end with an abrupt awakening. After awakening, the patients feel refreshed and continue their activities.
The state of absence or loss of attention individuals with somnolepsy experience may differ from individual to individual. This state of absence may besides from being described as a somnoleptic seizure also being described as a complex partial sleep syndrome. The most prominent feature is a fleeting loss of consciousness, during which the patients gradually lose the ability to perceive or react on external inputs, such as talking, reading or watching TV. The patients experience that they have a feeling of being in a bell jar or passing into a closed tunnel. Furthermore, some patients report other symptoms of sleepiness differing from patient to patient in frequency and intensity such as: sleep craving, excessive jwing, problems with keeping their eyes open and loss of concentration, blurred vision and problems with coordination when writing with a pencil or on a computer. After a seizure some of the patients tell that they had written absolute nonsense if they had been working with a computer. Some individuals are able to break off the condition by starting physical activity, or if people talk loudly to them, or if they are exposed to a sudden serious fright, such as hitting the side of the road when driving a car. Some patients are also able to break off the seizure (complex partial sleep syndrome) by closing their eyes for less than one minute or two. Afterwards they usually feel refreshed.

Based on a study of about 300 individuals with the tentative diagnosis of sleep apnoea, the inventor of the present invention estimates that the prevalence of somnolepsy is about 1 to 3% of the population.

Of the 300 individuals examined in this study about one half of the individuals were diagnosed as having sleep apnoea. This distribution is usual in Danish and international investigations. The other half of the group of individuals were carefully examined and divided into two groups of approximately the same size. One of the groups had well defined explanations of their sleep disorders, such as another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder, or simply bad sleep habits. The second group was eventually diagnosed as suffering from somnolepsy.

The prevalence of sleep apnoea is about 2 to 4% of the population. Therefore, the present inventor estimates on basis of this study that the prevalence of somnolepsy is about 1 to 3% of the population.
Somnolepsy is characterized by the following symptoms:

- Normal length of night sleep, but with many short awakenings during the night, typically 15-30 awakenings during the night. The REM sleep periods appear at normal times during the night sleep. The slow wave sleep (stages 4 and 3) is reduced.

- No sleep drunkenness at wake-up time.

- A decreased sleep latency measured by MSLT (multiple sleep latency test). Individuals with somnolepsy have a sleep latency between 30 seconds and 9 minutes, the mean value of the sleep latency for patients having somnolepsy has been measured to be $3.0 \pm 2.7$ minutes.

- Sleep onset REM periods were not registered during the MSLT's.

- Little excessive daytime sleepiness. The degree of daytime sleepiness is less compared to other sleep disorders, but tends to increase with disease duration.

- Individuals with somnolepsy have no cataplexy, hypnogogic hallucinations, sleep paralysis or hypnapompic hallucinations.

- Patients with somnolepsy have not been observed to have restless legs, sleep apnoea or periodic leg movements.

The symptomatology of somnolepsy cannot be explained by any other hitherto known sleep disorder.

The somnoleptic seizures characterizing somnolepsy appear in all situations like sleep attacks in other disorders and are especially dangerous for the person who gets the seizure and others when the seizure appears during work with a machine or when driving a motor vehicle. It is absolutely disadvantageous when a person gets a somnoleptic seizure/sleep attack during an important meeting or when being with friends, colleagues or family.

Therefore the condition needs an acute treatment of the seizure with a fast acting composition, easy to administer as soon as a seizure starts and before it develops into an uncontrollable state.

**Description of sleep terminology**

The term "night sleep" as used herein, may also be referred to as a "nocturnal sleep" and is in the context of the present application the same.

A normal length of night sleep refers to the length of sleep a person without any sleep disorder is having during the night. A normal length of night sleep is 8 hours +/- 2 hours. Individuals having a prolonged night sleep will sleep for at least 10 hours during the night, and most often more than 12 hours during the night.

The term "sleep drunkenness" as used herein refers to a state where individuals, when they are awake, appear to be partially asleep, confused or drunk. Sleep drunkenness can occur during the transition between sleep and wakefulness and is characterized as a disturbance of consciousness occurring on sudden arousal from sleep, characterized by confusion, disorientation and a misinterpretation of reality. Such loss of reality may in some instance lead to serious aggression, including homicidal behaviour. Confusion and sleep drunkenness are common after morning awakening and also after naps.

Polysomnography is a diagnostic test measuring physiological variants during a night sleep. The polysomnography is performed using a nocturnal polysomnogram (PSG), which is used to evaluate the sleep stages and sleep disturbance leading to sleep fragmentation, including sleep-related breathing disorder (SRBD), periodic limb movement of sleep (PLMS), rapid eye movement (REM)-sleep behaviour disorder, and/or more rarely seen, nocturnal seizures.
To objectively evaluate the degree of daytime sleepiness of an individual, a multiple sleep latency test (MSLT) is performed. Sleep latency is measured by a polysomnogram.

5 MSLT is a method of measuring the degree of daytime sleepiness of an individual. The MSLT measures the tendency to fall asleep in quiet situations. The MSLT consists of four or five 20-minute polysomnographically monitored daytime nap opportunities in a sleep laboratory bed in a dark quiet room with instructions to fall asleep, separated by 2-hour intervals wherein the patient is kept awake. The primary assessments made by the MSLT are the rapidity of sleep onset (sleep latency), which correlates to the degree of sleepiness, and to establish the presence of SOREMP (sleep onset REM periods) if sleep occurs during the nap opportunity. REM sleep episodes which are periods of sleep, during which dreams occur, at or close to sleep onset are known as sleep-onset rapid eye movement (SOREM) periods.

A MSLT latency refers to the result of a Multiple Sleep Latency Test (MSLT). A mean sleep latency over 10 minutes, such as 10 to 20 minutes, has generally been considered indicative of normal alertness, i.e. for people with a normal sleeping condition, whereas a mean sleep latency below 10 minutes is abnormal and less than 5 minutes is very abnormal.

A night sleep normally proceeds in cycles of REM sleep and four stages of non-REM sleep (NREM), wherein the order normally is:

\[
\text{Stages } 1 > 2 > 3 > 4 > 3 > 2 > \text{REM}
\]

In humans, a person will normally during a night sleep pass through these periods of sleep and the above cycle is on average 90 to 110 minutes, with a greater amount of stages 3 and 4 early in the night and more REM sleep later in the night. The first REM period normally appears after 90 minutes sleep.

30 NREM sleep accounts for 75-80% of total sleep in normal human adults and encompasses four stages, where stages 1 and 2 are considered "light sleep" and stages 3 and 4 are considered "deep sleep" or slow-wave sleep (SWS). In NREM sleep, there is relatively little dreaming.
REM periods appear 3-5 times during the night lasting 10 to 30 minutes. The number of REM periods decreases with age. REM-sleep or a REM-period within the first 20 minutes of sleep is abnormal and is called "sleep onset REM" (SOREM) or "sleep onset REM period" (SOREMP). In the context of this application SOREM and SOREMP may be used interchangeably and refer to the same state.

Cataplexy is characterised by sudden loss of bilateral muscle tone often provoked by strong emotions that are usually positive, such as laughter, pride, elation, or surprise. Negative emotions such as anger may also occasionally be a trigger. Cataplexy can be localized, or it can include all areas, most commonly the knees, face, and neck. The duration of cataplexy is usually short, ranging from a few seconds to several minutes at most, and recovery is immediate and complete.

Cataplexy may vary in pattern, frequency and severity. The loss of muscle tone ranges from a mild sensation of weakness, e.g. with head drop, facial sagging, jaw weakness, slurred speech, and buckling of the knees to a complete immediate postural collapse. Twitches and jerks may occur, particularly in the face, as the patient is trying to fight the episode.

Cataplexy must be differentiated from cataplexy-like episodes that are occasionally observed in normal individuals. For example, it is not uncommon for normal individuals to experience some form of muscle weakness in the context of exercise or sex. These episodes should not be considered typical cataplexy. Similarly, some individuals feel weak when stressed or tensed or may have the feeling that they have to roll on the floor when they are laughing uncontrollably. This also should not be considered cataplexy. Studies have shown that, in genuine cataplexy, the muscle episodes generally occur with significant frequency and are often triggered by typical situations, most commonly joking or laughing.

In addition, cataplexy should be differentiated from hypotension, transient ischemia attacks, drop attacks, akinetic seizures, neuromuscular disorders, vestibular disorders, psychological or psychiatric disorders, and sleep paralysis.

Hypnagogic hallucinations are vivid perceptual experiences typically occurring at sleep onset, while hypnopompic hallucinations occur at the sleep-to-wake
transition. Both individuals with hypnagogic- and hypnopompic hallucinations experience a realistic awareness of the presence of someone or something, and include visual, tactile, kinetic, and auditory phenomena. The accompanying affect is often fear or dread. Hallucinatory experiences such as being caught in a fire, impending attack by a stranger, or flying through the air are commonly reported.

Hypnagogic hallucinations are different from sleep onset rumination, which is less vivid and less visual. Furthermore, hypnagogic- and hypnopompic hallucinations are different from dreams and nightmares, which occur during ongoing sleep and not at sleep onset or the sleep-to-wake transition.

Some normal sleepers may experience hypnagogic or hypnopompic hallucinations a few times in their lives. However, for hypnagogic or hypnopompic hallucinations to be a significant symptom, these must occur regularly.

Sleep paralysis is a transient, generalized inability to move or to speak during the transition between sleep and wakefulness. The individual usually regains muscular control within several minutes. Sleep paralysis is a frightening experience, particularly when initially experienced, and is often accompanied by a sensation of an inability to breathe. Episodes often occur with hypnagogic hallucinations, and thus the frightful emotional is intensified.

Individuals having somnolepsy do not have symptoms of sleep paralysis. In contrast, sleep paralysis is experienced by 40% to 80% of narcoleptic patients.

Occasionally, episodes of sleep paralysis may be experienced by normal people, especially after a dream or nightmare in the middle of the night. In these cases, the individual awakens from a nightmare and tries to call out while going in and out of a dream. To be considered a significant symptom, sleep paralysis must occur regularly at sleep onset or awakening, not simply on an occasional basis during the middle of the night in association with dreaming.

Sleep paralysis must be distinguished from generalized fatigue and difficulties in waking up.
Daytime sleepiness or excessive daytime sleepiness (EDS) is the inability to stay awake and alert during the day, resulting in unintended lapses into either drowsiness or sleep attacks and is a common symptom for all sleep disorders. The term sleepiness is often mistaken for tiredness in everyday language.

As mentioned above, tiredness and sleepiness are often confused. There is no clear-cut definition of the two conditions. However, tiredness is mostly defined as a condition following a physically exhausting activity e.g. work and sport. Sleepiness is a condition where an individual feels an overwhelming desire to sleep. There are situations where it is difficult to distinguish between the two conditions e.g. a person who has worked for 20 hours is probably tired as well as sleepy.

Individuals having somnolepsy are characterized by experiencing seizures where they go through a state of transition from being awake, to not being attentive, passing through loose absence with fleeting loss of consciousness with or without merging into a short refreshing sleep.

Sleep attack is defined as an unintentional onset of sleep or involuntary sleep episode which usually cannot be interrupted or prevented unless medicated. The onset of a sleep attack is always forewarned to a certain extent. However this forewarning may be of varying duration in various sleep disorders.

The condition of merging into sleep as in somnoleptic seizures has a forewarning over a longer period of time than with sleep attacks in other sleep disorders (aura phenomena) and may be interrupted, e.g. by a loud noise. The somnoleptic seizures in somnolepsy thus differ from sleep attacks in individuals having narcolepsy, idiopathic hypersomnia, sleep apnoea, and other sleep disorders leading to excessive daytime sleepiness and sleep attacks.

Another type of sleep disorder where the individuals fall involuntarily asleep during the daytime is idiopathic hypersomnia. However, the daytime irresistible sleep attacks which occur to people having idiopathic hypersomnia are different from somnoleptic seizures, since they are long lasting, and not refreshing.
In table 1, the symptoms of sleep apnoea, idiopathic hypersomnia and narcolepsy are compared to the symptoms of somnolepsy. As explained above and evident from table 1, somnolepsy is a type of sleep disorder with symptoms different from any known type of sleep disorder. There is therefore a need for a fast release and

| Table 1: Diagnostic criteria of different sleep disorders, including somnolepsy |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Apnoea /hypopnoea during sleep                  | Many            | 0               | 0               | 0               |
| Oxygen saturation during sleep                   | Reduced         | normal          | normal          | normal          |
| Restless night sleep with many awakenings (PSG)  | ++              | 0 -> +          | +++             | +++             |
| Length of night Sleep                            | Prolonged       | prolonged + or normal | Normal   | normal          |
| Sleep periods during daytime, length and effect  | long 1-2 h. not refreshing | long 2-4 h. not refreshing | short refreshing | Short refreshing |
| Excessive daytime sleepiness (EDS)               | +++             | +++             | ++              | +               |
| Daytime sleep periods: warning periods with or without aura symptoms | 0 -> +         | 0 -> +          | 0 -> +          | +++             |
| Daytime sleep periods: irresistible/ interruptable | no/yes         | yes/no          | yes/no          | no/yes          |
| MSLT: sleep latency                             | can be reduced | reduced i.e. 6min+/- | low i.e.3min+/- | Low i.e.3min+/- |
| MSLT: REM periods                               | 0               | 0 -> 2          | 2 or more       | 0               |
| Cataplexy                                       | 0               | 0               | yes / 0         | 0               |
| Hypnagogic hallucinations and sleep paralysis   | 0               | 0               | Yes             | 0               |
| Prevalence                                      | 4 -> 6 %        | less than 0.02 % | 0.02->0,2 %     | 2 -> 3 %        |
| Nightly REM sleep                               | Normal          | Normal          | Abnormal        | Normal          |
fast acting composition for treatment of somnoleptic seizures and/or sleep attacks.

One object of the present invention is therefore to provide a composition which will be able to treat or prevent individuals who suffer from somnoleptic seizures from merging into sleep and individuals who suffer from sleep attacks to fall asleep.

The treatment of somnoleptic seizures and sleep attacks according to the present invention is an acute treatment used only when the individuals are in need thereof. In contrast, drugs known in prior art used in treatment of sleep disorders characterized by the patient having sleep attacks are administrated as prophylactic treatment, so that the drugs are given to the patients continuously over the day. Further, the known drugs comprising methylphenidate are not suitable for acute treatment, because of their latency to onset of action. For example the commercially available products, Ritalin has when administrated alone an onset of action of 15-20 minutes after administration, while the products Modate, Modafinil and Concerta have the onset of action of 30-60 minutes after administration (see http://www.leeheymd.com/charts/adhd_l.html disclosing "Medications for attention deficit hyperactivity disorders" by Kevin Leehey, M.D., 1980).

When using a vasodilator in a fast release and fast acting composition having an onset of effect within 30 to 60 seconds after administration, in prevention or treatment of somnoleptic seizures and/or sleep attacks, it is possible to prevent the individuals from falling involuntarily asleep and consequently prevent the danger for that individual or his or her surroundings. However, the effect only lasts for 20 to 30 minutes. The effect can be prolonged using a CNS-stimulating drug (CNS-stimulant).

The onset of action of the immediate release CNS-stimulant, methylphenidate, is within 15 to 20 minutes and the duration of action is 3 to 4 hours. This treatment can be repeated if the patients are in need thereof or combined with a sustained release formulation.
Fast acting vasodilating drugs e.g. glyceryl trinitrate have previously not been used for acute treatment of sleep attacks, or for prophylactic treatment of sleep disorders.

In one embodiment of the invention, the fast onset of effect is provided by administering the vasodilating agent in a sublingual mouth spray or a sublingual resoriblet.

In another embodiment of the invention, the fast onset and lasting effect are obtained by administering the vasodilating agent in combination with a CNS-stimulant, e.g. methylphenidate immediate release tablets. In some further embodiments of the present invention, the vasodilating agent and the CNS-stimulant are administered as a combination in a pharmaceutical composition, wherein both agents are contained in one single dosage form. In another embodiment of the invention, the CNS-stimulant and the vasodilating agent are co-administered as separate dosage forms.

A further object of the present invention is to use a combination of a vasodilating agent and a CNS-stimulant to prevent individuals from falling involuntary asleep e.g. when they are in extreme situations, such as driving a car for many hours, e.g. 5 hours or more, or have been awake for many hours, for example 20-24 hours or more.

The term "treatment" includes any effect, e.g. lessening, reducing, modulating, or eliminating, that results in the improvement of the condition, disease, disorder, etc. "treating" or "treatment" of a disorder state including: (1) inhibiting the disorder state, i.e., arresting the development of the disorder state or its clinical symptoms; or (2) relieving the disorder state, i.e., causing temporary or permanent regression of the disorder state or its clinical symptoms.

The term "prevention" or "preventing" as used herein means preventing the disease state, i.e., causing the clinical symptoms of the disease state not to develop in an individual that may be exposed to or predisposed to the disease state, but does not yet experience or display symptoms of the disease state.
The term "disorder state" means any disease, condition, symptom, or indication.

In the context of the present application, the term "in combination with" refers to administration in a single dosage form as one pharmaceutical composition containing both the vasodilating agent and the CNS-stimulant, as well as the administration of the vasodilating agent and the CNS-stimulant as separate dosage forms, either simultaneously or sequentially.

A vasodilating agent as described in the present application refers to an agent that can elicit the physiological response of dilating capillaries or other blood vessels in an individual following administration of the agent to the individual. Thus, a vasodilator causes vasodilation which refers to the widening of blood vessels resulting from relaxation of smooth muscle cells within the vessel walls. When blood vessels dilate, the flow of blood is increased due to a decrease in vascular resistance. Thus, when a drug is administered sublingually, such as in a sublingual mouth spray or sublingual resoriblet, the onset of action is faster than when the drug is administered enterically. Fast acting vasodilators have not previously been used for acute treatment of sleep attacks or treatment of sleep disorders.

In the context of the present application, the terms "a vasodilating agent" and "a vasodilator" refer to the same. Examples of vasodilating agents are amyl nitrite, glyceryl trinitrate, erythrityl tetranitrate, isosorbide dinitrate, isosorbide mononitrate, isosorbide 5-mononitrate, mannitol hexanitrate, pentaerythrityl tetranitrate, amlodipine, diltiazem, nifedipine, nisoldipine, verapamil, papaverine and cilostazol, and combinations thereof.

In an embodiment of the invention, the vasodilating agent is an acute vasodilating agent.

In a further embodiment of the invention, the vasodilating agent is an acute oral vasodilating agent.

In a preferred embodiment of the invention, the vasodilating agent is glyceryl trinitrate.
Another aspect of the invention is to provide a composition comprising an acute vasodilating agent and a CNS-stimulant.

5 The onset of action of different vasodilating agents is varying. Some vasodilating agents has a fast onset of action within 30 to 60 seconds and some other vasodilating agents, such as cutaneous vasodilating agents, has a slow onset of action, such as within 30 to 60 minutes.

10 In the context of the present invention, the term "acute vasodilating agent" refers to a vasodilating agent which has a fast onset of action within 30 to 60 seconds.

In an embodiment of the invention, the acute vasodilating agent is glyceryl trinitrate, isosorbide mononitrate or isosorbide trinitrate, preferably glyceryl trinitrate.

Glyceryl trinitrate

Glyceryl trinitrate is a fast acting vasodilating agent, well known in the art for treatment of constrictions in the coronary arteries of the heart in patients suffering from angina pectoris.

Glyceryl trinitrate is well known in the art and has the following formula:

\[ \text{CH}_2 - \text{ONO}_2 \]

\[ \text{CH} - \text{ONO}_2 \]

\[ \text{CH}_2 - \text{ONO}_2 \]

In the context of the present invention, the vasodilator may be administrated orally, bucally, sublingually, nasally, pulmonarily, transdermal, intravenously, subcutaneously, intramuscularly and rectally.
In preferred embodiments, the vasodilator is administrated orally, such as in form of a capsule, a tablet, a pill, a powder, a spray, a solution, a syrup or a suspension. Furthermore, the vasodilator may be administrated orally by an inhaler, such as for example a pump or aerosol inhaler.

In another embodiment of the invention, the vasodilator is administrated nasally, e.g. by using a nasal spray.

In a presently preferred embodiment, the vasodilator is administrated sublingually, such as in the form of a sublingual mouth spray or a sublingual resoriblet.

In one embodiment of the present invention the vasodilator, glyceryl trinitrate, is administered in a fast acting form, such as in the form of a sublingual spray or a sublingual resoriblet.

When administered sublingually glyceryl trinitrate is absorbed almost completely through the sublingual mucosa and acts within 30 seconds to 1 minute from the time of administration. The half life of glyceryl trinitrate (T½) in plasma is 3 to 5 minutes. Maximal effect is seen within 5 minutes and the duration of action is 20 to 30 minutes.

In a preferred embodiment of the present invention, glyceryl trinitrate is present in a fast acting sublingual spray comprising 0.4 mg or 0.8 mg glyceryltrinitrate dissolved in alcohol (less than 100 mg per dose). The spray may furthermore comprise peppermint oil, propellant gas and/or miglyol 829.

In another preferred embodiment of the present invention, glyceryl trinitrate is present in a fast acting sublingual resoriblet comprising 0.25 mg or 0.5 mg glyceryl trinitrate in magnesiumstearate, talcumpowerd, agar microcrystallic cellulose and lactosemonohydrate.

In another embodiment of the invention, the vsodilating agent is isosorbide mononitrate.
In still another embodiment of the invention, the vasodilating agent is isosorbide dinitrate.

In an embodiment of the present invention, isosorbide mononitrate is present in a fast acting sublingual spray comprising 10 mg or 20 mg isosorbide mononitrate dissolved in alcohol (less than 100 mg per dose). The spray may furthermore comprise peppermint oil, propellant gas and/or miglyol 829.

In another embodiment of the present invention, isosorbide mononitrate is present in a fast acting sublingual resoriblet comprising 30 mg or 60 mg isosorbide mononitrate in magnesiumstearate, talcumpowder, agar microcrystallic cellulose and lactosemonohydrate.

In an embodiment of the present invention, isosorbide dinitrate is present in a fast acting sublingual spray comprising 5 mg or 20 mg isosorbide dinitrate dissolved in alcohol (less than 100 mg per dose). The spray may furthermore comprise peppermint oil, propellant gas and/or miglyol 829.

In another embodiment of the present invention, isosorbide dinitrate is present in a fast acting sublingual resoriblet comprising 5 mg or 20 mg isosorbide dinitrate in magnesiumstearate, talcumpowder, agar microcrystallic cellulose and lactosemonohydrate.

A CNS-stimulant as described in the present application is a compound which is able to stimulate the central nervous system. A CNS-stimulant is a compound interfering with the balance between excitatory and inhibitory systems of the brain by modulating this balance which is normally maintained within relatively narrow limits. During treatment this balance should be drawn in the desired direction without serious side effects.

As described herein, the term "CNS-stimulant" may also be referred to as "central nervous system stimulant", or "central nervous system stimulator".

The CNS stimulant may be derived from natural sources or be synthetic.
The term "CNS-stimulant" shall include the base form of the CNS-stimulant, pharmaceutically acceptable salts thereof, stereoisomers thereof, ethers and esters thereof, and mixtures of any of the foregoing.

Examples of the CNS-stimulants which can be used in the present invention are methylphenidate, ethylphenidate, amphetamine, methamphetamine, amphetaminil, fenetylline, dextroamphetamine, phentermine, benzphetamine, phendimetrazine, diethylpropion, mazindol, fenfluramine, sibutramine, phenylpropanolamine, ephedrine, phenylephedrine, mephentermine, norepinephrine, epinephrine, caffeine, doxapram, modafinil, selegiline, pharmaceutically acceptable salts thereof and combinations thereof.

In a presently preferred embodiment of the invention, the CNS-stimulant is methylphenidate or a pharmaceutically acceptable salt thereof.

Methylphenidate is a chiral molecule of the formula (I):

\[
\text{O} \quad \text{O} \\
\text{H} \\
\text{N}
\]

Methylphenidate exists as four separate optical isomers, the L-threo, D-threo, D-erythro and L-erythro form and the systematic name is methyl 2-phenyl-2-(2-piperidyl)acetate.

Methylphenidate has a short elimination half-life of about 2-3 hours in adults.

In the context of the present invention, methylphenidate is in the form of one of the isomers or a racemate of two or more of the isomers.

In a presently preferred embodiment of the invention the CNS-stimulant is D-threo-methylphenidate.
Generally, a pharmaceutically acceptable salt of methylphenidate or another CNS-stimulant is used.

A "pharmaceutically acceptable salt" of a compound means any salt that retains the activity of the parent compound and does not impart any additional deleterious or untoward effects on the subject matter to which it is administered and in the context in which it is administered compared to the parent compound. As used herein, a "pharmaceutically acceptable salt" of a CNS-stimulant, such as methylphenidate, refers to a derivative of the CNS-stimulant wherein the CNS-stimulant is modified by making acid or basic salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkali or organic salts of acidic residues such as carboxylic acids, and the like.

Pharmaceutical acceptable salts of a CNS-stimulant, e.g. methylphenidate, may include salts of pharmaceutically acceptable organic or inorganic bases, such as, for example, salts from mono or polyvalent ions, such as lithium, sodium, potassium, calcium, and magnesium hydroxide or chloride. Organic salts may be made with amines, particularly ammonium salts such as mono-, di- and trialkyl amines or ethanol amines. Examples of organic salts may be, but are not limited to, ammonium, lysine, arginine, cysteine, meglumine, piperazine, diethylamine, benzathine or 4-phenylcycloesylamine. Hydrochlorid acid or some other pharmaceutically acceptable acid may form a salt with a compound that includes a basic group, such as amine or a pyridine ring.

Methylphenidate hydrochloride is presently preferred as a pharmaceutically acceptable salt of methylphenidate.

The pharmaceutically acceptable salts of the present invention may be synthesized from methylphenidate or another CNS-stimulant by conventional methods. Generally, such salts can be prepared by react the free acid or base form for example of the methylphenidate compound with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two.
CNS-stimulants are soluble in water or alcohol.

The blood-brain barrier is difficult to penetrate in that it requires compounds to be both lipophilic and hydrophilic at the same time. Compounds with known CNS-effect such as CNS-stimulants have this unique property. For several classes of CNS active substances it has been found that the activity and thus the penetration over the blood-brain barrier is optimal for log $P_0$ (octanol) values in the range of 1.5 - 2.7 with a mean value of 2.1. Log $P_0$ (octanol) property value is the ratio of the respective concentrations of a compound in the octanol and water partitions of a two-phase system at equilibrium. The concentration measurements are made at a constant temperature, normally 25° C. The Log P formula is:

$$\text{Log } P = \text{Log } \left[ \frac{[X]_{\text{oct}}}{[X]_{\text{aq}}} \right],$$

where the subscripts "oct" and "aq" refers to the octanol and water phases respectively.

In an embodiment according to the invention, the CNS-stimulant, such as methylphenidate, amphetamine, methamphetamine, amphetaminil, epinephrine and modafinil is soluble in alcohol.

In the context of the present invention, the CNS-stimulant may be administered orally, bucally, sublingually, nasally, pulmonary, transdermally, intravenously, subcutaneous, intramuscularly and rectally.

In a presently preferred embodiment, the CNS-stimulant is administered orally, such as in form of a capsule, a tablet, a pill, a powder, a spray, a solution, a syrup or a suspension. Alternatively, the CNS-stimulant may be administered orally by an inhaler, such as for example a pump or aerosol inhaler.

In another embodiment of the invention, the CNS-stimulant is administered nasally, e.g. by using a nasal spray.

In one embodiment, the CNS-stimulant is administered sublingually, such as in the form of a sublingual mouth spray or a sublingual resoriblet.
In the context of the present application, the term "sublingual administration" is defined as the administration form where a drug comes in contact with the mucous membrane beneath the tongue, and it diffuses through it. Because the connective tissue beneath the mucous membrane contains a profusion of capillaries, the drug then diffuses into them and enters the venous circulation. In contrast, many substances absorbed in the intestines are subject to "first pass metabolism" in the liver before entering the general circulation.

Thus, sublingual administration has certain advantages over enteric administration. Being more direct, the action is often faster, since it ensures that the substance will risk degradation only by salivary enzymes before entering the bloodstream, whereas enteric administered drugs must survive passage through the hostile environment of the gastrointestinal tract (GI tract), which risks degrading them, either by stomach acid or bile, or by the many enzymes therein, such as monoamine oxidase (MAO). Furthermore, after absorption from the gastrointestinal tract, such drugs must pass to the liver, where they may be extensively altered; this is known as the first pass effect of drug metabolism. Due to the digestive activity of the stomach and intestines and the solubility of the GI tract, the enteric route is unsuitable for certain substances.

Since individuals having somnoleptic seizures or sleep attacks are characterized by being forewarned before falling into sleep, one object of the present invention is to provide a fast acting composition comprising at least one vasodilating agent.

The onset of effect is within 30 to 60 seconds after administration so that the individuals, when the forewarning is experienced, may take the composition and preventing that they fall asleep. The duration of the effect is 20 to 30 minutes. This effect can be maintained for several hours by adding a well known CNS-stimulant to the composition.

In one aspect of the present invention, at least one vasodilating agent is used for acute prevention or treatment of somnolepsy, somnoleptic seizures and/or sleep attacks.
In one embodiment of the invention, at least one vasodilating agent and at least one CNS-stimulant is used for prevention or treatment of somnolepsy, somnoleptic seizures and/or sleep attacks.

5 In an embodiment of the invention, the vasodilating agent is an acute vasodilating agent.

A further aspect of the present invention is a composition comprising at least one acute vasodilating agent and at least one CNS-stimulant. Hereby is obtained an onset of effect within 30 to 60 seconds after administration lasting for minimum 3 to 4 hours.

In one embodiment of the invention, the fast acting composition is in the form of a sublingual mouth spray or a sublingual resoriblet.

15 In a further embodiment of the present invention, the composition comprising a combination of an acute vasodilating agent and a CNS-stimulant may be in the form of a single dosage form containing both the vasodilating agent and the CNS-stimulant or in the form of two separate dosage forms which are co-administered to provide the composition of the invention.

The term "co-administered" as used in the present application refers to the two drugs being administered in separate dosage forms. The co-administration can be simultaneous, or sequential. In sequential administration, either the CNS-stimulant or the vasodilating agent is administered first and the other agent is administrated immediately thereafter. In some embodiments, the vasodilating agent may be administered within a specific time period, e.g., several minutes or even hours after the administration of the CNS-stimulant. Where the vasodilating agent and the CNS stimulant are administered separately, the number of doses of each agent given per day may be different.

In one embodiment of the invention, the vasodilating agent and the CNS-stimulant are administered sequentially.
In a further embodiment of the invention, the CNS-stimulant and the vasodilating agent are administered simultaneously.

The term "immediate after" refers in the context of the present application to within 5 minutes, such as within 2 minutes, preferably within 1 minute, such as within 30 seconds.

In one embodiment of the invention, the composition comprising at least one vasodilating agent and at least one CNS-stimulant is administered as a combination pharmaceutical composition, wherein both drugs are contained in a single dosage form.

In another embodiment of the present invention, glyceryl trinitrate and methylphenidate are contained in a single dosage form.

In another embodiment of the present invention, the composition comprising the vasodilating agent and the CNS-stimulant are provided by co-administering separate dosage forms.

Formulations comprising CNS-stimulants, such as methylphenidate or modafinil, known from prior art to be used for treatment of individuals having narcolepsy or idiopathic hypersomnia are immediate release, sustained release, controlled release or modified release formulations. These prior art products are as described earlier characterized by having an onset of action of 15-60 minutes after administration. Further, some of the known products releases the drug over a longer period of time, making them suitable if a longer lasting prophylactic effect is necessary. This leads to intake of a higher daily dose of the drug.

However, individuals having somnoleptic seizures or sleep attacks, experience these attacks with varying frequencies. Thus, they usually do not need a sustained release, modified or controlled release formulation, but an immediate release and fast acting formulation, with onset of action within 30 to 60 seconds and lasting 3 to 4 hours to maintain the acute effect of the vasodilating agent for a sufficient time span.
In the context of the present invention, the term "a fast acting composition" refers to a composition of active ingredients that provides effect of the active ingredients immediately after administration of the composition, in particular within 1 minute after administration, such as within 30 seconds, preferably within 15 seconds.

In many embodiments of the invention, the fast release and fast acting composition further comprises one or more ingredient selected form the group consisting of a diluent, a carrier, a flavouring agent, a filler, a disintegrating and a lubricant.

In some embodiments of the invention, the fast release and fast acting composition is in the form of a tablet or pill and comprises in addition to the active drug substance other components such as a filler, a disintegrating agent, a water scavenging agent and/or a lubricant.

The composition may furthermore comprise one or more of the ingredients selected from the group consisting of stabilizers, antioxidants, buffering agents, foaming agents, pigments, colouring agents, bulking agents, sweetening agents, and fragrances.

Examples of fillers include but are not limited to lactose, sucrose, dextrose, sodium chloride, sorbitol, mannitol, urea, silicon dioxide, titanium dioxide, alumina, talc, kaolin, powdered cellulose and microcrystalline cellulose.

The disintegrating agent is used to facilitate disintegration of the composition. Examples of disintegrating agents include but are not limited to starches, such as corn starch, or potato starch, clays, celluloses, aligns, gums and crosslinked polymers.

Lubricants are used to facilitate the manufacturing process. Examples of lubricants include, but are not limited to, vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil, and oil of theobrom, glycerine, magnesium stearate, calcium stearate, and stearic acid.

The antioxidant may be citric acid.
The water scavenger may be silicon dioxide.

In the context of the present invention, the term "a fast acting composition" refers to a composition comprising active ingredients, where at least one of the active ingredients are released and act immediately after administration of the composition, in particular within 5 minutes after administration, such as within 3 minutes, in particular within 2 minutes such as within 1 minute and most preferably within 30 seconds.

In the context of the present invention, the dosage form of the composition can independently be selected from the group consisting of oral, buccal, sublingual, nasal, pulmonary, transdermal, intravenous, subcutaneous, intramuscular and rectal dosage forms.

In a presently preferred embodiment, the composition according to the present invention is administered orally, preferably in a suitable solid or liquid carrier or diluent to form a capsule, a tablet, a pill, a powder, a solution, syrup, or suspension. Furthermore, the composition may be administered orally by an inhaler, such as for example a pump or aerosol inhaler.

In a presently preferred embodiment, the composition is a tablet, pill or spray designed to be released and act fast by placing it sublingually in the oral cavity of the mouth or administered through a mouth spray.

In an embodiment of the invention, the composition is administered nasally, e.g. by using a nasal spray. For nasal administration, either a solid or liquid carrier can be used.

In a preferred embodiment of the invention, the composition is administered in the form of a sublingual tablet, such as a resoriblet, or a sublingual spray.

In the context of the present application the term "oral administration" may be referred to as "oral ingestion".

In an embodiment of the invention, the fast release and fast acting composition is in a single dosage in the form of a tablet, pill, capsule and the like and comprises
beside glyceryl trinitrate and methylphenidate a binder or filler such as tragacanth, acacias, corn starch or gelatine; an excipient such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, or alginic acid; a lubricant such as magnesium stearate; and/or a sweetening agent such as sucrose, lactose, saccharin, xylitol, and the like.

In an embodiment of the invention, the composition is a capsule and contains in addition to the above mentioned materials a liquid carrier such as fatty oil.

In an embodiment of the invention, the composition is administered by pulmonary administration, e.g., by administration of an aerosol formulation containing the active agent from, for example, a manual pump spray, nebulizer or pressurised metered-dose inhaler.

The term "pulmonary" as used herein refers to any part, tissue, or organ whose primary function is gas exchange with the external environment, e.g., O2/CO2 exchange, within an individual or patient. "Pulmonary" typically refers to the alveoli and the tissue of the respiratory tract. Thus, the term "pulmonary administration" refers to administering the composition according to the present invention to any part, tissue or organ whose primary function is gas exchange with the external environment, such as the alveoli.

The fast acting composition of the present invention can be administrated as appropriate depending on the need.

The fast release and fast acting composition of the present invention ensures release and acting of an effective amount of a vasodilating agent within 1 minute, preferably within 30 seconds, such as within 15 seconds after administration.

In one embodiment of the invention, the fast release and fast acting composition comprises a vasodilator such as glyceryl trinitrate and a CNS-stimulant, such as methylphenidate, which is to be used for the treatment of sleep disorders, in particular for the treatment of somnolepsy, by means of prevention of somnoleptic seizures and/or sleep attacks.
The term "effective amount" as used herein, refers to an amount of the compound, or a combination of compounds, which is sufficient to provide a desired therapeutic effect when administered alone or in combination to an individual in need of a treatment, to ameliorate symptoms arising from a sleep disorder, e.g. result in the fact that an individual is not merging into sleep. For example, an effective amount may be an amount of a vasodilator and methylphenidate present in a composition provided to give to a recipient patient or individual sufficient amount of the vasodilator and methylphenidate to elicit biological activity, such as staying awake.

The vasodilating agent according to the present invention is administered to an individual in an amount equipotent to the dose of 0.1 mg to 1.0 mg glycercy trinitrate. The vasodilating agent may be administered together with the CNS-stimulant in a single dosage form or in the form of co-administration of separate dosage forms comprising the vasodilator and the CNS-stimulant, respectively. In an embodiment of the invention, the vasodilating agent glycercy trinitrate is used in an amount from about 0.1 mg to about 1.0 mg of glycercy trinitrate, preferably from about 0.1 mg to about 0.8 mg, such as from about 0.1 mg to about 0.15 mg, preferably from about 0.15 mg to about 0.5 mg, such as from about 0.2 mg to about 0.5 mg, even more preferably from about 0.25 mg to about 0.5 mg.

In one embodiment of the invention, the vasodilating agent isosorbide mononitrate is used in an amount from about 10 mg to about 120 mg, preferably in an amount from about 10 mg to about 100 mg, such as from about 20 mg to about 100 mg, even more preferably in an amount from about 20 mg to about 80 mg, such as in an amount from about 30 mg to about 60.

In another embodiment of the invention, the vasodilating agent, isosorbide dinitrate is used in an amount from 1 mg to about 50 mg, preferably in an amount from 2 mg to about 40 mg, such as from about 2.5 mg to about 20 mg, even more preferably in an amount from about 5 mg to 20 mg. A composition according to the present invention comprising isomorbide dinitrate may be administered to an individual up to three times a day, so that the total amount of
isosorbide dinitrate administered to an individual per day does not exceed 120 mg.

In still another embodiment of the invention, the vasodilating agent, erythrityltetra nitrate is used in an amount from 1 mg to about 20 mg, preferably in an amount from 2 mg to about 15 mg, such as from about 5 mg to about 10 mg. A composition according to the present invention comprising erythrityltetra nitrate may be administered to an individual up to three times a day, so that the total amount of erythrityltetra nitrate administered to an individual per day does not exceed 30 mg.

In a further embodiment of the invention, the vasodilating agent, pentaerythritol is used in an amount from 5 mg to about 80 mg, preferably in an amount from 5 mg to about 40 mg, such as from about 10 mg to about 40 mg. A composition according to the present invention comprising pentaerythritol may be administered to an individual up to four times a day, so that the total amount of pentaerythritol administered to an individual per day does not exceed 160 mg.

The effective amount of a CNS-stimulant to be administered to an individual will vary depending on which CNS-stimulant is used, on the mode of administration and co-administered compounds, and the characteristics of the subject, such as general health, other diseases, age, sex, genotype, body weight, tolerance to drugs and medical condition of the individual or patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. The skilled artisan will be able to determine appropriate dosages depending on these and other factors.

The CNS-stimulant according to the present invention is administered to an individual in an amount equipotent to the dose of 0.1 mg to 60 mg methylphenidate. The CNS-stimulant may be administered together with a vasodilating agent in a single dosage form or in the form of co-administration of separate dosage forms comprising the CNS-stimulant and the vasodilator, respectively.
The term "an amount equipotent to" refers in the context of the present application to an amount which gives the same therapeutically effect.

Effective amounts of methylphenidate typically range between 0.1-60 mg, such as from 0.1-30 mg, preferably 0.1-20 mg, and even more preferably from 1-20 mg.

In an embodiment of the invention, the CNS-stimulant methylphenidate is used in an amount from about 0.01 mg to about 20 mg of methylphenidate, preferably from about 0.01 mg to about 10 mg, such as from about 0.2 mg to about 10 mg, preferably from about 0.2 mg to about 5 mg, such as from about 0.5 mg to about 5 mg, in particular from about 0.5 mg to about 4 mg, such as from about 0.5 mg to about 3 mg, preferably from about 0.5 mg to about 2 mg.

When methylphenidate is used as the CNS-stimulant, the amount of methylphenidate administered to an individual per day should not exceed 100 mg.

Methylphenidate according to the present invention would generally be used in the amount of 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 7 mg, 10 mg, 15 mg or 20 mg in each dosage.

In another embodiment of the invention, the CNS-stimulant modafinil is used in an amount from about 50 mg to about 600 mg of modafinil in each dosage, preferably from about 50 mg to about 400 mg, such as from about 75 mg to about 300 mg, preferably from about 100 mg to about 200 mg.

The amount of modafinil administered to an individual per day should not exceed 600 mg.

In another embodiment of the invention, amphetamine is used as the CNS-stimulant. Amphetamine is used in an amount from about 0.5 mg to about 20 mg, preferably from about 1 mg to about 15 mg, such as from about 3 mg to about 15 mg, preferably from about 5 mg to about 15 mg. Administration of a composition comprising amphetamine as the CNS-stimulant should not be repeated more than three times a day, since doses above 50 mg a day may cause adverse effects.
In another embodiment of the invention, epinephrine is used as the CNS-stimulant. Epinephrine is used in an amount from about 10 mg to 120 mg, preferably from about 10 mg to about 100 mg, such as from about 20 mg to about 80 mg, preferably from about 30 mg to about 60 mg. Administration of a composition comprising epinephrine as the CNS-stimulant should not be repeated more than three times a day, since doses above 200 mg a day may cause adverse effects.

In still another embodiment of the invention, metamphetamine is used as the CNS-stimulant. Metamphetamine is used in an amount from about 0.5 mg to about 20 mg, preferably from about 1 mg to about 15 mg, such as from about 3 mg to about 15 mg, preferably from about 5 mg to about 10 mg. Administration of a composition comprising metamphetamine as the CNS-stimulant should not be repeated more than three times a day, since doses above 50 mg a day may cause adverse effects.

In one embodiment of the present invention, the composition comprises a vasodilating agent in an amount equipotent to the dose of 0.1 to 1.0 mg glyceryl trinitrate, and a CNS-stimulant in an amount equipotent to the dose of 0.1 mg to 60 mg methylphenidate.

In another embodiment according to the invention, the composition comprises a vasodilating agent in an amount equipotent to the dose of 0.2 to 0.6 mg glyceryl trinitrate, and a CNS-stimulant in an amount equipotent to the dose of 1 mg to 20 mg methylphenidate.

An object of the present invention is to administer the CNS-stimulant to an individual only when it is necessary. It is an object of the invention that an individual quickly intakes the vasodilating agent in combination with a CNS-stimulant when a forewarning of a sleep attack is observed, and thus avoid falling into sleep. The forewarning may for example be experienced in connection with somnoleptic seizures by individuals suffering from somnolepsy or by individuals suffering from other disorders leading to sleep attacks, or any individual being sleepy, e.g. due to exposure to extreme situations, like driving a car for many hours.
The invention will now be described in further details in the following non-limiting examples.

5 Examples

In the following examples formulation of drugs are described wherein the amounts of only one tablet or only one spray flask are disclosed. However, when manufacturing the desired tablets or mouth sprays large batches are normally used concomitant with all the conventional quality control test required when producing medicinal products for human use. Thus the amount of compression and compression time vary according to batch sizes, equipment used, manufacturing facilities, etc. Thus, the examples listed below merely serve as examples of one possible way of performing the production steps.

15 Example 1

Formulation of a resoriblet comprising methylphenidate

The following is a suitable formulation of a 100 mg resoriblet comprising methylphenidate (1 mg or 5 mg):

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate</td>
<td>1 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>24.25 mg</td>
</tr>
<tr>
<td>Talcumpowder</td>
<td>10.75 mg</td>
</tr>
<tr>
<td>Agar microcrystallic cellulose</td>
<td>32 mg</td>
</tr>
<tr>
<td>Lactosemonohydrate</td>
<td>32 mg</td>
</tr>
</tbody>
</table>

The formulation comprising methylphenidate is prepared by mixing the ingredients and blending the composition for about 15 minutes in a suitable blender followed by direct compression at about 2500 psi for about 30 seconds on a Carver Press with a conventional circular flat faced tablet punch.

Example 2

Formulation of a mouth spray comprising methylphenidate
The following is a suitable formulation of a mouth spray comprising 1 mg or 5 mg methylphenidate per dose. The spray contains approximately 11.2 g in total and delivers 48 mg solution per pump with the spray (the spray comprises at least 200 doses):

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Methylphenidate</th>
<th>Ethanol</th>
<th>Miglyol® 829</th>
<th>Pepermint oil</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>233.3 mg</td>
<td>4966.7 mg</td>
<td>5500 mg</td>
<td>500 mg</td>
</tr>
<tr>
<td></td>
<td>1166.7 mg</td>
<td>4033.3 mg</td>
<td>5500 mg</td>
<td>500 mg</td>
</tr>
</tbody>
</table>

The formulation is prepared by solubilising the methylphenidate in ethanol, followed by adding the remaining ingredients and micronizing the resultant solution for about 5 minutes before filling and packing the resulting solution into a suitable container to be used with an appropriate valve e.g. an aerosol valve.

**Example 3** Formulation of a resoriblet comprising glyceryl trinitrate

The following is a suitable formulation of a 100 mg resoriblet comprising glyceryl trinitrate (0.25 mg or 0.5 mg):

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Glyceryl trinitrate</th>
<th>0.25 mg</th>
<th>0.50 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnesium stearate</td>
<td>25 mg</td>
<td>25 mg</td>
<td></td>
</tr>
<tr>
<td>Talcumpowder</td>
<td>10.75 mg</td>
<td>10.50 mg</td>
<td></td>
</tr>
<tr>
<td>Agar microcrystalline cellulose</td>
<td>32 mg</td>
<td>32 mg</td>
<td></td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td>32 mg</td>
<td>32 mg</td>
<td></td>
</tr>
</tbody>
</table>

The formulation comprising glyceryl trinitrate is prepared by mixing the ingredients and blending the composition for about 15 minutes in a suitable blender followed by direct compression at about 2500 psi for about 30 seconds on a Carver Press with a conventional circular flat faced tablet punch.

**Example 4**

Formulation of a mouth spray comprising glyceryl trinitrate
The following is a suitable formulation of a mouth spray comprising 0.40 mg or 0.80 mg glyceryl trinitrate per dose. One "pump" with the spray equals one dose. The spray flask contains approximately 11.2 g in total and delivers 48 mg solution per pump with the spray (the spray comprises at least 200 doses):

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyceryl trinitrate</td>
<td>93.3 mg</td>
</tr>
<tr>
<td>Ethanol</td>
<td>5106.7 mg</td>
</tr>
<tr>
<td>Miglyol® 829</td>
<td>5500 mg</td>
</tr>
<tr>
<td>Pepermint oil</td>
<td>500 mg</td>
</tr>
</tbody>
</table>

The formulation is prepared by solubilising the glyceryl trinitrate in ethanol, followed by adding the remaining ingredients and micronizing the resultant solution for about 5 minutes before filling and packing the resulting solution into a suitable container to be used with an appropriate valve e.g. an aerosol valve.

**Example 5**

**Formulation of resoriblet comprising glyceryl trinitrate and methylphenidate**

The following is a suitable formulation of a 100 mg resoriblet comprising 0.25 mg or 0.5 mg glyceryl trinitrate and 1 mg or 5 mg methylphenidate i.e. a total of 1.25 mg or 5.5 mg drug in each resoriblet:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyceryl trinitrate</td>
<td>0.25 mg</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>1 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>24.25 mg</td>
</tr>
<tr>
<td>Talcumpowder</td>
<td>10.50 mg</td>
</tr>
<tr>
<td>Agar microcrystallic cellulose</td>
<td>32 mg</td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td>32 mg</td>
</tr>
</tbody>
</table>

The formulation is prepared by mixing the ingredients and blending the composition for about for 15 minutes in a suitable blender followed by direct compression at about 2500 psi for about 30 seconds on a Carver Press with a conventional circular flat faced tablet punch.
Example 6
Formulation of a mouth spray comprising glyceryl trinitrate and methylphenidate

The following is a suitable formulation of a mouth spray comprising 0.40 mg or 0.80 mg glyceryl trinitrate and 1 mg or 5 mg methylphenidate per dose. Hence, one "pump" with the spray equals one dose consisting of either 0.4 mg glyceryl trinitrate and 1 mg methylphenidate or 0.8 mg glyceryl trinitrate and 5 mg methylphenidate. The spray contains approximately 11.2 g in total and delivers 48 mg solution per pump with the spray (the spray comprises at least 200 doses):

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyceryl trinitrate</td>
<td>93.3 mg</td>
<td>186.7 mg</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>233.3 mg</td>
<td>1166.7 mg</td>
</tr>
<tr>
<td>Ethanol</td>
<td>4873.4 mg</td>
<td>4846.6 mg</td>
</tr>
<tr>
<td>Miglyol® 829</td>
<td>5500 mg</td>
<td>4500 mg</td>
</tr>
<tr>
<td>Pepermint oil</td>
<td>500 mg</td>
<td>500 mg</td>
</tr>
</tbody>
</table>

The formulation is prepared by solubilising the glyceryl trinitrate and methylphenidate in ethanol, followed by adding the remaining ingredients and micronizing the resultant solution for about 5 minutes before filling and packing the resulting solution into a suitable container to be used with an appropriate valve e.g. an aerosol valve.

Example 7
Formulation of a resoriblet comprising epinephrine

The following is a suitable formulation of a 200 mg resoriblet comprising epinephrine (30 mg or 60 mg):

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>30 mg</td>
<td>60 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>20 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td>Talcumpowder</td>
<td>10 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Agar microcrystallic cellulose</td>
<td>66 mg</td>
<td>49.5 mg</td>
</tr>
<tr>
<td>Lactosemonohydrate</td>
<td>74 mg</td>
<td>60.5 mg</td>
</tr>
</tbody>
</table>
The formulation comprising epinephrine is prepared by mixing the ingredients and blending the composition for about 15 minutes in a suitable blender followed by direct compression at about 2500 psi for about 30 seconds on a Carver Press with a conventional circular flat faced tablet punch.

Example 8
Formulation of a mouth spray comprising epinephrine

The following is a suitable formulation of a mouth spray comprising 10 mg epinephrine per pump with spray. To obtain 30 mg or 60 mg of epinephrine defined as one dose it is required to "pump" three times (30 mg) or six times (60 mg) with the spray to arrive at said dose. The spray flask contains approximately 11.2 g in total and delivers 48 mg solution per pump with the spray (the spray comprises solution for at least 200 pumps):

- Epinephrine 2333.3 mg
- Ethanol 4866.7 mg
- Miglyol® 829 3500 mg
- Peppermint oil 500 mg

The formulation is prepared by solubilising the epinephrine in ethanol, followed by adding the remaining ingredients and micronizing the resultant solution for about 5 minutes before filling and packing the resulting solution into a suitable container to be used with an appropriate valve e.g. an aerosol valve.

Example 9
Formulation of a resoriblet comprising methylamphetamine

The following is a suitable formulation of a 100 mg resoriblet comprising methylamphetamine (5 mg or 10 mg):

- Methylamphetamine 5 mg 10 mg
- Magnesium stearate 21 mg 16 mg
- Talcum powder 10 mg 10 mg
- Agar microcrystalline cellulose 32 mg 32 mg
- Lactose monohydrate 32 mg 32 mg
The formulation comprising methylamphetamine is prepared by mixing the ingredients and blending the composition for about 15 minutes in a suitable blender followed by direct compression at about 2500 psi for about 30 seconds on a Carver Press with a conventional circular flat faced tablet punch.

Example 10
Formulation of a mouth spray comprising methylamphetamine

10 The following is a suitable formulation of a mouth spray comprising 5 mg or 10 mg methylamphetamine per dose. One "pump" with the spray equals one dose. The spray flask contains approximately 11.2 g in total and delivers 48 mg solution per pump with the spray (the spray comprises at least 200 doses):

- Methylamphetamine 1166.7 mg 2333.3 mg
- Ethanol 4033.3 mg 4866.7 mg
- Miglyol® 829 5500 mg 3500 mg
- Pepermint oil 500 mg 500 mg

The formulation is prepared by solubilising the methylamphetamine in ethanol, followed by adding the remaining ingredients and micronizing the resultant solution for about 5 minutes before filling and packing the resulting solution into a suitable container to be used with an appropriate valve e.g. an aerosol valve.

Example 11
Formulation of a resoriblet comprising isosorbide mononitrate

25 The following is a suitable formulation of a 200 mg resoriblet comprising isosorbide mononitrate (30 mg or 60 mg):

- Isosorbide mononitrate 30 mg 60 mg
- Magnesium stearate 20 mg 20 mg
- Talcumpowerder 10 mg 10 mg
- Agar microcrystalline cellulose 66 mg 49.5 mg
- Lactosemonohydrate 74 mg 60.5 mg
The formulation comprising isosorbide mononitrate is prepared by mixing the ingredients and blending the composition for about 15 minutes in a suitable blender followed by direct compression at about 2500 psi for about 30 seconds on a Carver Press with a conventional circular flat faced tablet punch.

Example 12

Formulation of a mouth spray comprising isosorbide mononitrate

The following is a suitable formulation of a mouth spray comprising 10 mg isosorbide mononitrate per pump with spray. To obtain 30 mg or 60 mg of isosorbide mononitrate defined as one dose it is required to "pump" three times (30 mg) or six times (60 mg) with the spray to arrive at said dose. The spray flask contains approximately 11.2 g in total and delivers 48 mg solution per pump with the spray (the spray comprises solution for at least 200 pumps):

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isosorbide mononitrate</td>
<td>2333.3</td>
</tr>
<tr>
<td>Ethanol</td>
<td>4866.7</td>
</tr>
<tr>
<td>Miglyol® 829</td>
<td>3500</td>
</tr>
<tr>
<td>Peppermint oil</td>
<td>500</td>
</tr>
</tbody>
</table>

The formulation is prepared by solubilising the isosorbide mononitrate in ethanol, followed by adding the remaining ingredients and micronizing the resultant solution for about 5 minutes before filling and packing the resulting solution into a suitable container to be used with an appropriate valve e.g. an aerosol valve.

Example 13

Formulation of a resoriblet comprising isosorbide dinitrate

The following is a suitable formulation of a 100 mg resoriblet comprising isosorbide dinitrate (5 mg or 20 mg):

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isosorbide dinitrate</td>
<td>5 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>21 mg</td>
</tr>
<tr>
<td>Talcumpowder</td>
<td>10 mg</td>
</tr>
<tr>
<td>Agar microcrystallic cellulose</td>
<td>32 mg</td>
</tr>
<tr>
<td></td>
<td>20 mg</td>
</tr>
<tr>
<td></td>
<td>16 mg</td>
</tr>
<tr>
<td></td>
<td>10 mg</td>
</tr>
<tr>
<td></td>
<td>27 mg</td>
</tr>
</tbody>
</table>
The formulation comprising isosorbide dinitrate is prepared by mixing the ingredients and blending the composition for about 15 minutes in a suitable blender followed by direct compression at about 2500 psi for about 30 seconds on a Carver Press with a conventional circular flat faced tablet punch.

Example 14
Formulation of a mouth spray comprising isosorbide dinitrate

The following is a suitable formulation of a mouth spray comprising 5 mg or 10 mg isosorbide dinitrate per dose. To obtain 5 mg of isosorbide dinitrate defined as one dose it is required to "pump" once with the 5 mg isosorbide dinitrate spray to arrive at said dose. To obtain 20 mg of isosorbide dinitrate defined as one dose it is required to "pump" two times (20 mg) with the 10 mg isosorbide dinitrate spray to arrive at said dose. The spray flask contains approximately 11.2 g in total and delivers 48 mg solution per pump with the spray (the spray comprises solution for at least 200 pumps):

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>1166.7 mg</th>
<th>2333.3 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isosorbide dinitrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethanol</td>
<td>4033.3 mg</td>
<td>4866.7 mg</td>
</tr>
<tr>
<td>Miglyol® 829</td>
<td>5500 mg</td>
<td>3500 mg</td>
</tr>
<tr>
<td>Pepermint oil</td>
<td>500 mg</td>
<td>500 mg</td>
</tr>
</tbody>
</table>

The formulation is prepared by solubilising the isosorbide dinitrate in ethanol, followed by adding the remaining ingredients and micronizing the resultant solution for about 5 minutes before filling and packing the resulting solution into a suitable container to be used with an appropriate valve e.g. an aerosol valve.

Example 15
Formulation of a resoriblet comprising epinephrine and isosorbide mononitrate
The following is a suitable formulation of a 250 mg resoriblet comprising epinephrine (30 mg or 60 mg) and isosorbide mononitrate (30 mg or 60 mg):

- Epinephrine: 30 mg or 60 mg
- Isosorbide mononitrate: 30 mg or 60 mg
- Magnesium stearate: 20 mg or 20 mg
- Talcum powder: 10 mg or 10 mg
- Agar microcrystalline cellulose: 76 mg or 44.5 mg
- Lactose monohydrate: 84 mg or 55.5 mg

The formulation comprising epinephrine and isosorbide mononitrate is prepared by mixing the ingredients and blending the composition for about 15 minutes in a suitable blender followed by direct compression at about 2500 psi for about 30 seconds on a Carver Press with a conventional circular flat faced tablet.

**Example 16**

Formulation of a mouth spray comprising epinephrine and isosorbide mononitrate

The following is a suitable formulation of a mouth spray comprising 10 mg epinephrine and 10 mg isosorbide mononitrate per pump with spray. To obtain 30 mg of epinephrine and 30 mg isosorbide mononitrate defined as one dose it is required to "pump" three times with the spray to arrive at said dose. To obtain 60 mg of epinephrine and 60 mg isosorbide mononitrate defined as one dose it is required to "pump" six times with the spray to arrive at said dose. The spray flask contains approximately 11.2 g in total and delivers 48 mg solution per pump with the spray (the spray comprises solution for at least 200 pumps):

- Epinephrine: 2333.3 mg
- Isosorbide mononitrate: 2333.3 mg
- Ethanol: 5033.4 mg
- Miglyol® 829: 1250 mg
- Peppermint oil: 250 mg

The formulation is prepared by solubilising epinephrine and isosorbide mononitrate in ethanol, followed by adding the remaining ingredients and micronizing the resultant solution for about 5 minutes before filling and packing.
the resulting solution into a suitable container to be used with an appropriate valve e.g. an aerosol valve.

**Example 17**

5 **Formulation of a resoriblet comprising modafinil**

The following is a suitable formulation of a 300 mg resoriblet comprising 100 mg modafinil and a suitable formulation of a 600 mg resoriblet comprising 200 mg modafinil:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>100 mg</th>
<th>200 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modafinil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>21 mg</td>
<td>42 mg</td>
</tr>
<tr>
<td>Talcum powder</td>
<td>11 mg</td>
<td>22 mg</td>
</tr>
<tr>
<td>Agar microcrystalline cellulose</td>
<td>80 mg</td>
<td>160 mg</td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td>88 mg</td>
<td>176 mg</td>
</tr>
</tbody>
</table>

The formulation comprising modafinil is prepared by mixing the ingredients and blending the composition for about 15 minutes in a suitable blender followed by direct compression at about 2500 psi for about 30 seconds on a Carver Press with a conventional circular flat faced tablet punch.

20

**Example 18**

**Study of a group of about 300 individuals having sleep disorder**

A group of about 300 individuals who all by their general practitioner were suggested to have sleep apnoea were examined. All the individuals were CRM tested (Cardio respiratory monitoring) and about 50% of them were diagnosed as having sleep apnoea. The other half of the individuals was carefully examined and about half of them had well defined explanations of their sleep disorders, such as somatic or psychiatric diseases or medicine/drug abuse. The other half, one fourth of the group, was thoroughly examined clinically and by performing a polysomnografic test (PSG) and a multiple sleep latency test (MSTL). This group was eventually diagnosed as suffering from somnolepsy. They started prophylactic treatment with methylphenidate (30 mg per day) and 3 to 4 weeks later the MSLTs were repeated. Afterwards, the treatment with methylphenidate was
withdrawn and 3 to 4 weeks later the MSLTs were performed again. The MSLTs were performed as a 4 x MSLT per day for all the individuals. The measured MSLT values are given in table 2:

Table 2:

<table>
<thead>
<tr>
<th></th>
<th>Mean sleep latency</th>
<th>Range of sleep latency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>3 minutes</td>
<td>0.5-9 minutes</td>
</tr>
<tr>
<td>During treatment</td>
<td>8.7 minutes</td>
<td>3.5-17.4 minutes</td>
</tr>
<tr>
<td>After treatment</td>
<td>2.8 minutes</td>
<td>0.4-7.5 minutes</td>
</tr>
</tbody>
</table>

It is shown in the table that treatment with methylphenidate increases mean sleep latency upward the level of a normal mean sleep latency. Furthermore, a significant clinical improvement in the individuals sleep disorder (somnolepsy) is observed when treated prophylactically with methylphenidate.

Furthermore, the MSLTs showed that no SOREMP sleep was registered in any of the patients. As many of the individuals from example 18 only suffered from somnoleptic seizures/sleep attacks once or twice a day, it would be suitable to use acute treatment only when they suffered from sleep attacks. Methylphenidate immediate releases tablets were not suitable for acute treatment as the latency to onset of action is 15 to 20 minutes. Therefore, a study was performed on patients treated with glyceryl trinitrate, which is shown in example 19.
Example 19

A group of 10 patients from example 18 were treated with glyceryl trinitrate in a formulation containing 0.4 mg in a sublingual spray or 0.5 mg in a sublingual resoriblet. The patients reported a very fast effect of the drug on their sleepiness, from about 30 seconds to about 1 minute after the drug was administered. However, they told that the action of the drug disappeared after approximately 20 to 30 minutes and that the sleep attack came back.

Example 20

Clinical evaluation of acute treatment of a somnoleptic seizures/sleep attacks in a group of 22 individuals using glyceryl trinitrate in combination with methylphenidate.

A group of 22 individuals suffering from somnoleptic seizures were treated with glyceryl trinitrate in combination with methylphenidate. Glyceryl trinitrate was administered in a dose of 0.4 mg dissolved in alcohol when a sublingual spray (Glytrin) was used. The spray furthermore comprised peppermint oil, propellant gas and/or miglyol 829. 0.25 mg or 0.5 mg glyceryl trinitrate was administrated when sublingual fast acting resoriblets were used. Further ingredients of the resoriblets are magnesium stearate, talcum powder, agar microcrystallic cellulose and lactosemonohydrate. Shortly after the administration of the vasodilating agent, methylphenidate was administered as a 10 mg immediate release tablet (Ritalin). If the individuals studied were experiencing more than 1 somnoleptic seizure a day, they were allowed to repeat this treatment up to 4 times a day.

The results of this treatment of somnoleptic seizures with the fast acting combination of a vasodilating agent and a CNS-stimulant showed that it is effective and safe. The onset of action was reported by the individuals treated to be very fast and was registered to be within 30 to 60 seconds after the administration of the drugs. Similar results were seen when treating sleep attacks in patients suffering from other sleep disorders.

This means that individuals suffering from invalidating and dangerous sleep attacks and somnoleptic seizures can reduce the treatment of the disease to only
simultaneous when they suffer from a somnoleptic seizure or a sleep attack, and thereby avoid a continuous daily treatment with a CNS-stimulant as known in prior art. If in some cases, treatment becomes too frequent, e.g. more than 4 - 6 times per day, it was changed into a continuous prophylactic treatment with a CNS-stimulant, e.g. as described in example 18.

Example 21

Prophylactic with methylphenidate in two individuals suffering from somnolepsy.

1. individual
A 26-year-old man who has been a truckdriver since he was 18 had been experiencing an increasing number of "somnoleptic seizures" during the years. Nearly every day during the last year before treatment he had to stop the truck and rest or sleep for a few minutes. He had several times experienced to hit the roadside being very close to a serious accident. One day, during a somnoleptic seizure, he did not manage to stop and the truck hit the roadside and crashed. After that, he stopped as a truckdriver. His general practitioner (GP) suspected him to have sleep apnoea. However, he was examined by the inventor of the present invention and the examination revealed that he did not have sleep apnoea. Further investigations revealed that he had somnolepsy. He started prophylactic treatment with methylphenidate, and 3 weeks later, he was back in his job as a truckdriver, and did no longer experience sleep seizures. 9 months later, he was still driving his truck every day without seizures. However, for unknown reasons he stopped taking his medicine. Shortly thereafter he was killed in a traffic accident.

2. individual
A 22-year-old woman working as a shop assisent in a supermarket had during the last 2 to 3 years experienced the symptoms characteristic of somnoleptic seizures when she served customers. She got the habit to tell the customers that she would go to the stockroom looking for a better article or another excuse for running out of the store where she found a place to stand or sit, closing her eyes for a minute or two. Afterwards she returned, refreshed, to the customer continuing her sales job.
Her GP gave a very precise description of the condition and asked for advise as he was in doubt whether this otherwise healthy young woman could suffer from sleep apnoea.

The inventor of the present invention examined her and found that she did not suffer from sleep apnoea. The examinations revealed that she had somnolepsy. She began prophylactic treatment with methylphenidate, and at control visits to the sleep center 3 and 7 months later, she could tell that she was doing her job without somnoleptic seizures. She could now and then feel a little sleepy, but not to a degree that she had to leave her customers. Her treatment has now been changed to glyceryl trinitrate in combination with methylphenidate immediate release tablets to use only when she is in need for acute treatment.

**Example 22**

Acute treatment with glyceryl trinitrate spray in combination with methylphenidate immediate release tablets in two individuals, one of them suffering from somnoleptic seizures and the other suffering from residual sleep attacks despite treatment of his sleep apnoea with CPAP.

1. **Individual**

   A 32-year-old man, high-ranking in a trade union, suffered from a tendency to be absent and unable to follow the detailed negotiations at meetings. Sometimes he would merge into sleep, unless he was pushed in the side by one of his colleagues, who were aware of his problem. He suffered from somnoleptic seizures, and was successfully treated with the fast acting combination of 0.4 mg glyceryl trinitrate sublingual spray followed by a 10 mg methylphenidate immediate release tablet (Ritalin).

2. **Individual**

   A 55-year-old man suffered from sleep apnoea. He was treated during the night with CPAP (continous positive airway pressure) with good effect. After some months he again complained of sleepiness and sleep attacks during the daytime 3 to 4 times a week despite CPAP treatment. He was treated with the fast acting combination of glyceryl trinitrate sublingual spray and 10 mg methylphenidate immediate release tablets.
immediate release tablet (Ritalin) these few times a week. The treatment was effective and he could prevent the sleep attacks.
Claims

1. At least one vasodilating agent for acute prevention or treatment of somnoleptic seizures and/or sleep attacks.

2. At least one vasodilating agent according to claim 1, wherein said vasodilating agent is in combination with at least one CNS-stimulant.

3. At least one vasodilating agent in combination with at least one CNS-stimulant according to claim 2, wherein the vasodilating agent and the CNS-stimulant are present in a single dosage form.

4. At least one vasodilating agent in combination with at least one CNS stimulant according to claim 2, wherein the vasodilating agent and the CNS-stimulant are co-administrated as separate dosage forms.

5. At least one vasodilating agent according to claim 1, wherein said vasodilating agent is selected from the group consisting of amyl nitrite, glyceryl trinitrate, erythritol tetranitrate, isosorbide dinitrate, isosorbide mononitrate, isosorbide 5-mononitrate, mannitol hexanitrate, pentaerythritol tetranitrate, amlodipine, diltiazem, nifedipine, nisoldipine, verapamil, papaverine and cilostazol, pharmaceutically acceptable salts thereof and combinations thereof.

6. At least one vasodilating agent according to any of the claims 1 to 5, wherein the vasodilating agent is glyceryl trinitrate.

7. At least one vasodilating agent in combination with at least one CNS stimulant according to any of the claims 2 to 4, wherein said CNS-stimulant is selected from the group consisting of methylphenidate, ethylphenidate, amphetamine, methamphetamine, amphetamine hydrochloride, fenetyl, dextroamphetamine, phenetermine, benzphetamine, phendimetrazine, diethylpropion, mazindol, fenfluramine, sibutramine, phenylpropanolamine, ephedrine, phendimetrazine, mephenetermine, norepinephrine, epinephrine, caffeine, doxapram, modafinil, selegiline, pharmaceutically acceptable salts thereof and combinations thereof.
8. At least one vasodilating agent in combination with at least one CNS stimulant according to claim 7, wherein said CNS-stimulant is methylphenidate or a pharmaceutically acceptable salt thereof.

9. Use of at least one vasodilating agent for the preparation of a medicament for acute prevention or treatment of somnoleptic seizures and/or sleep attacks.

10. A composition comprising at least one acute vasodilating agent and at least one CNS-stimulant.
AMENDED CLAIMS
received by the International Bureau on 10 September 2009 (10.09.2009).

1. At least one vasodilating agent for acute prevention or treatment of sleep attacks,

2. At least one vasodilating agent according to claim 1, wherein said vasodilating agent is in combination with at least one CIMS-stimulant.

3. At least one vasodilating agent in combination with at least one CNS-stimulant according to claim 2, wherein the vasodilating agent and the CNS-stimulant are present in a single dosage form.

4. At least one vasodilating agent in combination with at least one CNS stimulant according to claim 2, wherein the vasodilating agent and the CNS-stimulant are co-administrated as separate dosage forms.

5. At least one vasodilating agent according to claim 1, wherein said vasodilating agent is selected from the group consisting of glyceryl trinitrate, erythrityl tetranitrate, isosorbide mononitrate, isosorbide 5-mononitrate, isosorbide dinitrate, isosorbide trinitrate, mannitol hexanitrate, pentaerythrityl tetranitrate and pharmaceutically acceptable salts thereof and combinations thereof.

6. At least one vasodilating agent according to any of the claims 1 to 5, wherein the vasodilating agent is glyceryl trinitrate.

7. At least one vasodilating agent in combination with at least one CNS stimulant according to any of the claims 2 to 4, wherein said CNS-stimulant is selected from the group consisting of methylphenidate, ethylphenidate, amphetamine, methamphetamine, amphetaminil, fenetylline, dextroamphetamine, phentermine, benzphetamine, phendimetrazine, diethylpropion, mazindol, fenfluramine, sibutramine and pharmaceutically acceptable salts thereof and combinations thereof.
8. At least one vasodilating agent in combination with at least one CNS stimulant according to claim 7, wherein said CNS-stimulant is methylphenidate or a pharmaceutically acceptable salt thereof.

9. Use of at least one vasodilating agent for the preparation of a medicament for acute prevention or treatment of somnoleptic seizures and/or sleep attacks.

10. A composition comprising at least one acute vasodilating agent selected from the group consisting of glyceryl trinitrate, erythrityl tetranitrate, isosorbide mononitrate, isosorbide 5-mononitrate, isosorbide dinitrate, isosorbide trinitrate, mannitol hexanitrate, pentaerythrityl tetranitrate and pharmaceutically acceptable salts thereof and combinations thereof and at least one CNS-stimulant selected from the group consisting of methylphenidate, ethylphenidate, amphetamine, methamphetamine, amphetamine, fenetylline, dextroamphetamine, phentermine, benzphetamine, phenidimetrazine, diethylpropion, mazindol, fenfluramine, sibutramine and pharmaceutically acceptable salts thereof and combinations thereof.
### A. CLASSIFICATION OF SUBJECT MATTER

INV. A61P25/00 A61K31/00 A61K31/21 A61K31/445 A61K45/06

According to International Patent Classification (IPC) or to both national classification and IPC

### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, EMBASE, BIOSIS

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C

Special categories of cited documents

A' document defining the general state of the art which is not considered to be of particular relevance

E' earlier document but published on or after the international filing date

L' document which may throw doubts on the priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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'Z' document member of the same patent family

Date of the actual completion of the international search: 3 July 2009

Date of mailing of the international search report: 15/07/2009

Name and mailing address of the ISA/Authorized officer

European Patent Office, P B 5818 Patentlaan 2 NL·2280 HV Rijswijk
Tel (+31-70) 340-2040, Fax (+31-70) 340-3016

Pacreu Largo, Marta
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