TREATMENT OF NEUROPATHIC PAIN, FIBROMYALGIA OR RHEUMATOID ARTHRITIS

Field of invention

The present invention relates to the use of Gaboxadol for the preparation of medicaments useful for the treatment of neuropathic pain, fibromyalgia or rheumatoid arthritis.

Background of the Invention

Neuropathic pain refers clinically to a group of chronic pain syndromes. They share the common feature that they are caused by an initial nerve damage, which subsequently results in an abnormal sensoric processing in the central and peripheral nervous system. Neuropathic pain conditions are the consequence of a number of diseases, e.g. diabetes, AIDS, multiple sclerosis, amputees and cancer. The available analgesic drugs do often produce insufficient pain relief. Tricyclic antidepressants and some antiepileptic drugs, e.g. gabapentin, lamotrigine and carbamazepine are efficient in some patients. However, there is still a large unmet need for efficient drugs for the treatment of these conditions.

Most types of persistent, chronic non malignant pain, including fibromyalgia and arthritic pain, are characterised by an increased blood level of pro inflammatory cytokines and a reciprocal relation between pain severity and sleep quality in that the pain interrupts sleep and this subsequently increase the pain sensation. These types of pain are characterised by prominent intrusion of alpha rhythms in the sleep EEG leading to an impaired slow wave sleep. Thus, if was possible to counteract the effects mediated via the cytokines or, conversely, normalize the sleep pattern, it might be possible to obtain both improved analgesic activity and improved sleep quality and thus, the synergy between these two mechanism might be able to improve the quality of life for these particular groups of patients

It has now, surprisingly, been found that Gaboxadol (THIP) described in EP Patent 0840601 B1, in the formalin pain model and in a dose dependent manner potently inhibited the pain response in phase 2. This second phase of the pain response, which is mediated via several proinflammatory mediators is thought to mimic some of the key features of neuropathic pain,

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fibromyalgia and rheumatoid arthritis, amongst others prolonged pain and reduced sensitivity to the strong opioid analgesics.

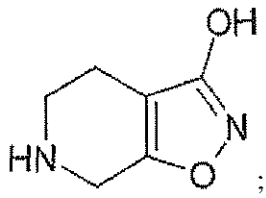
Description of the Invention

In a first aspect, there is provided a method for the preparation of a pharmaceutical composition for the treatment of neuropathic pain, in a subject, comprising: formulating an effective amount of gaboxadol for the treatment of neuropathic pain, and a pharmaceutically acceptable carrier.

In a second aspect, there is provided the use of Gaboxadol or a pharmaceutically acceptable salt thereof for the preparation of a medicament for the treatment of neuropathic pain.

There is disclosed a medicament for the treatment of neuropathic pain, fibromyalgia or rheumatoid arthritis.

More specifically, the disclosure relates to the use of Gaboxadol having the general formula



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or pharmaceutically acceptable salts thereof for the preparation of a medicament for the treatment of neuropathic pain, fibromyalgia or rheumatoid arthritis.

In one embodiment, the disclosure relates to the use of Gaboxadol or pharmaceutically acceptable salts thereof for the preparation of a medicament for the treatment of neuropathic pain.

In another embodiment, the disclosure relates to the use of Gaboxadol or pharmaceutically acceptable salts thereof for the preparation of a medicament for the

treatment of fibromyalgia.

In a further embodiment, the disclosure relates to the use of Gaboxadol or pharmaceutically acceptable salts thereof for the preparation of a medicament for the treatment of rheumatoid arthritis.

In a further embodiment, Gaboxadol or pharmaceutically acceptable salts thereof is selected from the zwitter ion, typically a hydrate thereof, although the anhydrate is also suitable. A typical embodiment is the zwitter ion monohydrate.

In a further embodiment, Gaboxadol or pharmaceutically acceptable salts thereof is selected from an acid addition salt, typically a pharmaceutically acceptable acid addition salt. A typical embodiment is an organic acid addition salt, such as any one of the maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethane-disulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-amino-benzoic, glutamic, benzene sulfonic or theophylline acetic acid addition salts. Another typical embodiment is an inorganic acid addition salt, such as any one of the hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric or nitric acid addition salts.

Typically, Gaboxadol or pharmaceutically acceptable salts thereof is in the form of the hydrochloric acid salt, the hydrobromic acid salt, or the zwitter ion monohydrate.

In a further embodiment, Gaboxadol or pharmaceutically acceptable salts thereof is crystalline, such as the crystalline hydrochloric acid salt, the crystalline hydrobromic acid salt, or the crystalline zwitter ion monohydrate.

There is also disclosed a method for the treatment of neuropathic pain, fibromyalgia or rheumatoid arthritis, comprising administering to an individual in need thereof a pharmaceutically acceptable amount of Gaboxadol or a pharmaceutically acceptable salt thereof.

Gaboxadol or a pharmaceutically acceptable salt thereof is administered as an oral dose form, such as a solid oral dose form, typically tablets or capsules, or as a liquid oral dose form. Gaboxadol is most conveniently administered orally in unit dosage forms such as tablets or capsules, containing the active ingredient in an amount from about 0.1 to about 150 mg/day, such as from about 0.1 to about 100 mg/day, about 0.5 to about 50 mg/day, from about 5 to about 50 mg/day, or from about 1 to about 5 mg/day. Typically, the pharmaceutical composition comprises from 2.5 mg to 20 mg, such as 5 mg to 15 mg of gaboxadol or a pharmaceutically acceptable salt thereof. The amount of Gaboxadol is calculated based on the free base form.

The individual, such as the human patient, to be treated with Gaboxadol may in fact be any subject of the human population, male or female, which may be divided into children, adults, or elderly. Any one of these patient groups relates to a disclosed embodiment.

According to thedisclosed embodiments, Gaboxadol may be used as the base (the zwitter ion) or as a pharmaceutically acceptable acid addition salt thereof or as an anhydrate or hydrate of such salt or base. The salts of the compound used in the invention are salts formed with non-toxic organic or inorganic acids. Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethane-disulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-amino-benzoic, glutamic, benzene sulfonic and theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromo-theophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids. Gaboxadol may also be used as the zwitter ion, e.g. the mono hydrate thereof.

The acid addition salts according to the disclosed embodiments may be obtained by treatment of Gaboxadol with the acid in an inert solvent followed by precipitation, isolation and optionally re-crystallisation by known methods and if desired micronisation of the crystalline product by wet or dry milling or another convement process, or preparation of particles from a solvent-emulsification process. Suitable methods are described in EP patent 0000338.

Precipitation of the salt is typically carried out in an inert solvent, e.g. an inert polar solvent such as an alcohol (e.g. ethanol, 2-propanol and n-propanol), but water or mixtures of water and inert solvent may also be used.

According to the disclosed embodiments, Gaboxadol or a pharmaceutically acceptable salt thereof may be administered in any suitable way e.g. orally or parenterally, and it may be presented in any suitable form for such administration, e.g. in the form of tablets, capsules, powders, syrups or solutions or dispersions for injection. Preferably, and in accordance with the purpose of

the present invention, Gaboxadol is administered in the form of a solid pharmaceutical entity, suitably as a tablet or a capsule or in the form of a suspension, solution or dispersion for injection.

Methods for the preparation of solid pharmaceutical preparations are well known in the art. Tablets may thus be prepared by mixing the active ingredients with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a convenient tabletting machine. Examples of adjuvants or diluents comprise: corn starch, lactose, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvant or additive such as colourings, aroma, preservatives, etc. may also be used provided that they are compatible with the active ingredients.

A suitable formulation of Gaboxadol is described in WO 02/094225 filed May 17, 2002. Without limiting the invention in any way, it is intended that any one of the aspects or embodiments of this patent application is suitable embodiments of the medicament or pharmaceutical compositions herein.

Pharmacological Tests

The formalin pain model is a well-established animal model of persistent somatic pain (Dubuisson, D. and Dennis, S.G. *Pain 4,* **1977**, 161-174). It has been described as a model of clinical inflammatory pain (Tjølsen, A. and Hole, K., *In: Dickenson, A.H. and Besson, J.-M.R., Editors,* **1997**. *The Pharmacology of Pain, Springer-Verlag, Berlin,* 1-20). Formalin injected subcutaneously in a hind paw produces initially a local stimulation of the nociceptors, this is referred to as phase 1. This is followed by inflammatory processes and nerve sensitisation (phase 2). The latter phase models the neuropathic pain condition. A number of drugs are active in the model, e.g. morphine and in particular antiepileptic drugs (e.g. gabapentine, lamotrigine, carbamazepine) that have shown beneficial effects in clinical neuropathic states. However, these treatments are accompanied by troublesome side effects. The non-steroid antiinflammatory drugs (NSAIDs) that are used for treatment of inflammatory processes in tissue and have relatively weak effects on neuropathic pain conditions have weak activity in the formalin model.

Experimental Procedure

Fifty microlitres of 2.5% formalin were administered s.c. into the plantar region of the right hind-paw. Following the injection, the animal was placed into an observation chamber, and its subsequent nociceptive behaviour observed. A mirror behind the observation chamber allowed the experimenter an unobstructed view of the injected paw. Observation of the animal's behaviour was made from 0-5 min (phase 1) and 20-30 min (phase 2) following formalin injection. The total time the animal spent licking, biting or shaking the injected paw was recorded. All animals (n=6-10) received a formalin injection and a s.c. injection of either vehicle or test drug 30 min or 2 h before the formalin test.

Results

The testing of Gaboxadol in the formalin pain model showed that the compound potently inhibited the pain response in phase 2, in a dose dependent manner.

Gaboxadol also showed potent and dose dependent inhibition of the pain response in phase 1.

Claims

1. A method for the preparation of a pharmaceutical composition for the treatment of neuropathic pain, in a subject, comprising: formulating an effective amount of gaboxadol for the treatment of neuropathic pain, and a pharmaceutically acceptable carrier.

2. The method of claim 1, wherein the gaboxadol is in the form of an acid addition salt, a zwitter ion hydrate, or a zwitter ion anhydrate.

3. The method of claim 2, wherein the acid addition salt is a hydrochloride salt or a hydrobromide salt.

4. The method of claim 2, wherein the zwitter ion hydrate is a zwitter ion monohydrate.

5. The method of claim 1, wherein the pharmaceutical composition is an oral dose form.

6. The method of claim 5, wherein the oral dose form is a solid oral dose form or a liquid oral dose form.

7. The method of claim 6, wherein the solid oral dose form is a tablet or a capsule.

8. The method of claim 1, wherein the gaboxadol is crystalline.

9. The method of claim 1, wherein the subject is a human.

10. The method of claim 1, wherein the effective amount of gaboxadol is from about 0.1 mg/day to about 50 gm/day.

11. The use of Gaboxadol or a pharmaceutically acceptable salt thereof for the preparation of a medicament for the treatment of neuropathic pain.

12. The use of claims 11 wherein the Gaboxadol is in the form of an acid addition salt, a zwitter ion hydrate, or zwitter ion anhydrate.

13. The used of claim 12 wherein the acid addition salt is hydrochloride or a hydrobromide salt.

14. The use of claim 12, wherein the zwitter ion hydrate is a zwitter ion monohydrate.

15. The use of any one of claims 11-14 wherein the Gaboxadol is in an oral dose form.

16. The use of claim 15 wherein the oral dose form is a solid oral dose form or a liquid oral dose form.

17. The use of claim 16 wherein the solid oral dose form is a tablet or a capsule.

18. The use of any one of claims 11-17 wherein said Gaboxadol is crystalline.

19. The use of any one of claims 11-18 wherein said pharmaceutical composition is for treating a human.

20. The use of any one of claims 11-19 wherein the Gaboxadol is in an amount from 0.1 mg/day to 50 mg/day.