EFFERVESCENT GAMMA-HYDROXYBUTYRIC ACID GRANULES

SUMMARY

In a first aspect, there is provided a granule comprising a solid core on which is supported an active ingredient, said active ingredient being selected from gamma-hydroxybutric acid or one of its pharmaceutically acceptable salts, said granule further comprising, supported on said solid core, the following compounds:

- one or more compounds which generate gas evolvement,
- one or more diluents,
- a binder
- a coating membrane

said granule being characterized in that the solid core represents from 15% to 50% by weight based on the total weight of the granule.

In a second aspect, there is provided a pharmaceutical composition comprising a mixture of granules as defined herein, wherein said mixture consists of two groups of granules (A) and (B), the granules (A) and the granules (B) having different kinetics for releasing the active ingredient.

In a third aspect, there is provided the use of the granule as defined herein in the manufacture of a medicament for treating pathologies requiring at least 85% in less than 5 minutes *in vivo* availability of GHB.

The object of the present invention is gamma-hydroxybutyric granules, as well as pharmaceutical positions containing them. Gamma-hydroxybutryic acid (GHB or sodium oxybate) is a natural metabolite present at the level of the brains of mammals; its chemical structure is close to gamma-aminobutryic acid (GABA), a neurotransmitter, whence its activity on the central nervous system.

This active ingredient was used as a general anesthetic and as a hypnotic in the treatment of insomnia. Presently it is especially used in certain sleep disorders, such as catalepsy in narcoleptic patients, under the commercial name of Xyrem®, in an amount of two night takings of solute. Within this scope, the patient takes an initial dose at bedtime and has to get up at about four hours later for a second night taking.

GHB is highly soluble, hygroscopic and strongly alkaline. The therapeutic doses are very high. Indeed, in the treatment of narcolepsy, the doses used range from 4.5 to 9 g of active ingredient per day.

Moreover, GHB is frequently used a recreational drug with different goals: deinhibition, relaxation, search for physical or sexual performances.

The whole of these characteristics show the benefit of having a prolonged release form of this active ingredient. Many studies were conducted in this direction. Thus, different oral prolonged release formulations may be reported in the prior art without however any of them providing a complete answer to the whole of this complex problem.

US 5,594,030 describes pharmaceutical compositions appearing as granules or tablets containing GHB in a cellulose matrix; these pharmaceutical preparations exhibit dissolution over a period from 7 to 8 hours.

EP 0 635 265 describes controlled release pharmaceutical compositions based on a salt of gamma-hydroxybutryic acid consisting of a core, in the form of granules or tablets, comprising the active ingredient dispersed in a cellulose matrix. A controlled release form is thereby obtained by diffusion through membranes aiming at a release of the active ingredient in the upper portion of the digestive tract.

Application US2006/210630 describes pharmaceutical compositions with controlled release of GHB consisting of particles comprising the active ingredient as a core. These particles are then covered with a protective layer, the latter being itself covered with a second layer for enteric release.

Immediate or gastro-protective particles are therefore known from