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(54) Title: AQUEOUS SUSPENSIONS OF 9-HYDROXYRISPERIDONE FATTY ACID ESTERS

(57) Abstract

The present invention is concerned with a pharmaceutical composition suitable as a depot formulation for administration via intramuscular or subcutaneous injection, comprising: (1) as an active ingredient a therapeutically effective amount of a 9-hydroxyrisperidone fatty acid ester or a salt, or a stereoisomer or a stereoisomeric mixture thereof and (2) a pharmaceutically acceptable carrier; wherein the pharmaceutically acceptable carrier is water and the active ingredient is suspended therein; and with a process of preparing such a composition. The invention further concerns such a pharmaceutical composition for use as a medicament in the treatment of schizophrenia, non-schizophrenic psychoses, behavioural disturbances associated with neurodegenerative disorders, e.g. in dementia, behavioural disturbances in mental retardation and autism, bipolar mania, depression, anxiety.

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AQUEOUS SUSPENSIONS OF 9-HYDROXYRISPERIDONE FATTY ACID ESTERS

The present invention is concerned with a pharmaceutical composition suitable as a depot formulation for administration via intramuscular or subcutaneous injection, comprising :

(1) as an active ingredient a therapeutically effective amount of a 9-hydroxy-risperidone fatty acid ester or a salt, or a stereoisomer or a stereoisomeric mixture thereof and

(2) a pharmaceutically acceptable carrier; wherein the pharmaceutically acceptable carrier is water and the active ingredient is suspended therein ;

and with a process of preparing such a composition. The invention further involves such a pharmaceutical composition for use as a medicament in the treatment of schizophrenia, non-schizophrenic psychoses, behavioural disturbances associated with neurodegenerative disorders, e.g. in dementia, behavioural disturbances in mental retardation and autism, bipolar mania, depression, anxiety.

Risperidone is generic to 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one. The preparation and pharmacological activity thereof are described in EP-0,196,132 (corresponding to US-4,804,663). Various conventional pharmaceutical dosage forms, including tablets, capsules, drops, suppositories, oral solutions and injectable solutions are exemplified therein. In practice, risperidone is normally administered as the base in a tablet or in a buffered, oral or intramuscular solution. Particular solutions for oral or intramuscular administration are described in WO-96/01652.

Risperidone is a highly potent drug having a relatively narrow therapeutic index. It may produce undesirable side effects on overdosage, most notably extra pyramidal syndrome (EPS) and to a lesser extent hypotension (due to peripheral alpha-adrenergic activity). For the purpose of producing an antipsychotic effect in a patient the total daily dose of risperidone ranges from about 2 to about 8 mg ; for the alleviation of behavioral disturbances associated with neurodegenerative disorders the total daily dose is usually less and typically ranges from about 0.5 to about 2 mg. Inter-individual differences and co-medication may necessitate dose titrating in patients.

For a number of reasons, it is desirable to administer risperidone in a sustained or delayed release (depot) formulation which is effective over an extended period of time,

preferably about 3 weeks or more.

WO-94/25460 (corresponding to EP-0,697,019) relates to a first such depot formulation and concerns the risperidone pamoate salt, a poorly water-soluble salt form of risperidone, which may be suspended in a pharmaceutically acceptable carrier, such as water or an oil, and may be administered subcutaneously or intramuscularly. This salt, however, has pharmacokinetic properties which are suboptimal. The release of the active ingredient from the formulations appears to be too rapid, which results in relatively high initial plasma levels and an inadequate mean duration of action, both characteristics which should be improved upon in a truly effective depot formulation.

WO-95/13814 concerns sustained release formulations for parenteral administration wherein risperidone is microencapsulated in a biocompatible, biodegradable wall-forming material (e.g. a polymer such as dl-(polylactide-co-glycolide)). The micro-encapsulated formulations have suitable pharmacokinetic properties, but require sophisticated processes of preparation in a purpose-built plant.

Consequently, there is still a need for an effective and readily available depot formulation of risperidone or a risperidone-like compound.

It is known that risperidone is metabolized to 9-hydroxyrisperidone which has a pharmacological profile and potency comparable with that of the parent drug risperidone, but which has a longer elimination half-life. Risperidone is distributed to and eliminated from the brain tissues more rapidly than its metabolite 9-hydroxy-risperidone. 9-hydroxyrisperidone, its enantiomeric forms and the C_{2-20} alkanoic acid esters thereof are described in EP-0,368,388 (corresponding to US-5,158,952 and US-5,254,556). Said esters are considered to be potentially valuable prodrugs of the active metabolite of risperidone for use in depot formulations.

In addition, the problems associated with the genetic polymorphism in the metabolism of risperidone to its active metabolite 9-hydroxyrisperidone can possibly be avoided by administration of the metabolite or a long-acting prodrug thereof, instead of risperidone itself.

Indeed, in the metabolism of risperidone, debrisoquine-type genetic polymorphism plays a distinct role. As a consequence, humans can be phenotyped as poor, intermediate or extensive metabolizers on the basis of their metabolic ratio. Said metabolic ratio is defined as the ratio of urine recovery of debrisoquine to that of the 4-hydroxymetabolite of debrisoquine over a period of 8 hours after an oral intake of

10 mg debrisoquine. In oriental people more than 99% of the population can be phenotyped as extensive metabolizers and poor metabolizers are rather seldom. In the Caucasian race however only about 90% of the population can be phenotyped as either extensive or intermediate metabolizers. Approximately 10% of the population are poor metabolizers and have deficient amounts of the debrisoquine-hydroxylase enzyme.

The duration of action and the peak plasma levels of active agents (risperidone and 9-hydroxyrisperidone) are dependent on the debrisoquine metabolic ratio of the human subject treated with risperidone. More in particular, in poor metabolizers high transient peak levels of risperidone are likely to be attained when the total daily amount is administered in a single dose. This may give rise to undesired side-effects such as extra pyramidal syndrome (EPS) and hypotension.

Further inter-individual differences among humans, as far as the metabolism of risperidone is concerned, are due to the fact that in clinical practice the human subjects to be treated with risperidone will usually receive additional medication, e.g. tranquillizers such as phenothiazines, neuroleptica such as haloperidol, antidepressiva etc., all of which may compete with risperidone for the debrisoquine-hydroxylase enzyme. These drug interactions may seriously affect the metabolism of risperidone, especially in extensive metabolizers, and may result in the occurrence of adverse effects in patients receiving such additional medication.

The present invention results from the investigations into the development of an efficient, well-tolerated, sustained or delayed release (depot) formulation of a 9-hydroxyrisperidone alkanoic acid ester which is therapeutically effective for at least three weeks or more. By the expression "effective for at least three weeks or more", one means that the plasma levels of the active ingredient, 9-hydroxyrisperidone (free alcohol liberated by hydrolysis from the alkanoic acid ester), should be above approximately 10 ng/ml. On the other hand, said plasma levels should remain at all times below a threshold value of approximately 100 ng/ml in order for one to call the formulation "efficient". The threshold value is the mean plasma level during a considerable period of time, e.g. for more than 15 minutes, above which patients may experience undesirable side effects, or conversely, the value of the plasma level under which the systemic tolerance of the formulation in question is still acceptable. The threshold value does not hold for transient, high plasm levels during a short period of time, e.g. for less than 15 minutes, which are due, for example to unexpected burst-release of the active ingredient.

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