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(54) Title: ORAL SUSPENSION FOR TREATING EOSINOPHILIC ESOPHAGITIS

(57) Abstract: Formulations of a stable budesonide high-viscosity oral suspension, suitable for the treatment of eosiniphilic esophagitis, formulated with ingredients of well established medicinal use. The formulations constitute examples for the manufacture of a therapeutic product which is easily administered or self-administered, thereby ensuring the best patient compliance.

# ORAL SUSPENSION FOR TREATING EOSINOPHILIC ESOPHAGITIS

This invention relates to a pharmaceutical formulation of a stable, high-viscosity corticosteroid, more specifically budesonide, suspension to be administered orally for the treatment of esophageal pathologies of immune origin and more specifically for the treatment of eosinophilic esophagitis, or esophageal eosinophilia, in both children and adults.

Eosinophilic esophagitis is a recently recognized disorder characterized by the accumulation of eosinophils or eosinophil granulocytes, i.e. white blood cells constituting one of the immune system components, in the esophagus. Symptoms of eosinophilic esophagitis frequently mimic those of gastroesophageal reflux disease, but the two diseases are quite different in terms of the histopathology and response to therapy. Eosinophilic esophagitis is an increasingly recognized cause of dysphagia and possibly heartburn that is unresponsive to antireflux measures. The annual incidence of eosinophilic esophagitis in children has been estimated to be in the order of 1:100,000, which makes this disease to be classified as a rare disease and the treatment to be termed as 'orphan'.

A number of treatments were demonstrated effective

in eliminating symptoms and reducing esophageal eosinophilia, each carrying its own risks and benefits and ease of compliance (i.e. the adherence of the patient to the medical therapy). Dietary elimination is safe and offers lifelong treatment, but compliance may be difficult. Topical steroids offer a valid alternative. Patients swallow a steroid based oral formulation, thus delivering a topical anti-inflammatory agent directly to the esophageal mucosa. Corticosteroids inhibit the synthesis and secretion of cytokines, known to influence eosinophil growth, differentiation and activation. Especially children, who are unresponsive to dietary restriction, or cannot tolerate a dietary treatment, clearly may benefit from orally administered corticosteroids. Indeed, swallowed topical steroids were shown to induce and maintain low esophageal eosinophil levels.

Administration of oral formulations of budesonide turns out to be particularly suitable for treating eosinophilic esophagitis because of its high local activity. Compared with beclomethasone dipropionate, the topical potency of budesonide is two-fold greater, and greater yet if compared with prednisone. Budesonide, administered orally, has an extensive first-pass metabolism in the liver with a residual bioavailability of only 11%. Budesonide is eliminated with the urine and faeces in the

form of its metabolites that are endowed with only a very slight corticosteroid activity.

Recently, a successful treatment of eosinophilic esophagitis was reported with the use of an oral viscous suspension of budesonide. In this trial children under the age of ten years received 1 mg/day of an oral viscous budesonide liquid suspension obtained by mixing just before administration two 0.5 mg/2 ml Pulmicort Respules; a water suspension of budesonide meant for inhalation purposes for treating asthma; with 5 grams of sucralose. Only one patient received double this dose.

An ideal formulation for an oral suspension is one that prolongs the contact of the active ingredient with the mucous membranes of the esophagus.

International Application published under the Patent Cooperation Treaty at No. WO 2009/132048 A2, having the title "TREATING EOSINOPHILIC ESOPHAGITIS", of Meritage Pharma, Inc. at San Diego, California, U.S.A., referred to as Document D1 hereinafter, discloses methods and compositions suitable for treating eosinophilic esophagitis. More specifically, D1 discloses methods that include orally administering a steroid, such as budesonide, together with a mucoadherent to a mammal such that eosinophilic esophagitis is treated, where a mucoadherent can be any compound that prolongs the contact of another

molecule, such as a steroid, to mucous membranes, e.g. to coat the surface of the esophagus. Compositions are disclosed in D1 containing a steroid and a mucoadherent. A delivery system is also disclosed in D1 including a syringe containing a composition having a steroid and a mucoadherent. The delivery system can contain a tube that allows a user to deliver the composition to the back of the patient's oral cavity.

Hyaluronic acid is envisaged in D1, which, however, is not only an excipient, but also an active principle.

The tube indicated as an advantage in D1, actually has the great disadvantage that a child cannot self-administer it and therefore it is necessary that an expert adult shall perform the not easy task of using the delivery device without irritating the patient. Moreover, such a complex manoeuvre may compromise compliance, which is an extremely important factor for this type of chronic patient.

The object of this invention is to provide a pharmaceutical formulation of a stable budesonide high-viscosity oral anti-inflammatory suspension for treating eosiniphilic esophagitis, that manages to penetrate esophageal wall and reaches eosinophiles with a steady absorption, formulated with ingredients of well established medicinal use. The oral suspension is easily administered

and even easily self-administered, thereby ensuring best compliance.

Therefore, it is the subject-matter of this invention the formulation of appended Claim 1.

It is also the subject-matter of this invention the formulation of appended Claim 2.

It is further the subject-matter of this invention the formulation of appended Claim 3.

It is still further the subject-matter of this invention the formulation of appended Claim 4.

This invention will be understood based on the following detailed disclosure of ways for formulating and carrying out it, only given as a matter of example, absolutely not of restriction.

Possible thickening agents that were taken into consideration were:

- Hypromellose (hydroxypropylmethylcellulose): this one is present in Aircort™ nasal spray, it is used as a thickening agent in ophthalmic preparations, but not in oral suspension;

- Methylcellulose: this one is recommended as a thickening agent in sugar-based suspension formulations, but it cannot be used because of its incompatibility with parabens;

- Avicel RC591 (microcrystalline cellulose/car-

boxymethylcellulose): already present in Peridon™ suspension, but it is primarily a suspending agent, rather than a thickening agent;

- PVP (polyvinylpyrrolidone): this one is recommended as a thickening agent in oral suspensions and solutions.

Placebo testing for identification of the optimal viscosity comprised:

- Hypromellose (ref.: RAYMOND C. ROWE (ed.), *Handbook of Pharmaceutical Excipients*, Royal Pharmaceutical Society, UK, 7th ed.);

- Avicel RC591 (ref.: *http://www.fmcbiopolymer.com/Pharmaceutical/Products/Avicelforsuspensions.aspx*);

- Polyvinylpyrrolidone (PVP K90) (ref.: *Handbook of Pharmaceutical Excipients* cit.).

One possible formulation would comprise a combination of the above mentioned excipients at various concentrations.

After various attempts, the following formulation was deemed to be a possible runner for the final formulation:

| |
|---|
| Polysorbate |
| Sorbitol solution (70% volume) |
| Methylparaben |

| |
|---|
| Propylparaben |
| Avicel RC591 |
| Polyvinylpyrrolidone (PVP K90) |
| Highly purified water *q.s.* to 100 ml |

This formulation was completed with the addition of budesonide as the active ingredient.

All physical tests gave satisfactory results as regards appearance, particle size, thixotropy, sedimentation, re-suspendibility, pH, density, viscosity, budesonide assay, methyl parahydroxybenzoate assay, propyl parahydroxybenzoate assay, related substances, unspecified impurity, total impurities and microbiological testing.

The bulk formulation was then distributed in 100 ml amber glass bottles and stored at ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) conditions for formal stability testing.

However, the two-month accelerated stability results highlighted a diminished preservative efficacy, as well as an abnormal oxidation of the active ingredient.

The above inconvenience was solved by the addition to the initial formulation of:

| **Ingredient** | **% weight/volume** |
|---|---|
| Disodium edetate (EDTA) | 0.009-0.011 |

| | |
|---|---|
| Sodium citrate dihydrate | 0.0045-0.0055 |
| Citric acid monohydrate | *q.s.* to pH 4.5 |

EDTA is primarily used as a chelating agent by forming stable water-soluble complexes (chelates) with alkaline earth and heavy metal ions, particularly copper, iron and manganese, which might otherwise catalyze auto-oxidative reactions.

Furthermore, EDTA has a recognised antimicrobial activity, which is used in combination with other antimicrobial preservatives due to its synergistic effects.

Sodium citrate dihydrate/citric acid monohydrate buffer was also added to adjust the pH of the suspension to pH 4.5, because the acid medium increases the preservative efficacy.

The resulting bulk formulation was tested against set specifications, distributed in 100 ml bottles and stored at ICH recommended conditions for stability testing. The active ingredient proved to be stable, but the anti-microbial activity was considered still not optimal because inactive for one of the contaminants: *Aspergillus niger*.

The addition was deemed necessary, due to the above results, of a further element with anti-microbial activity, and more specifically active against *Aspergillus niger*. Potassium sorbate was thus added to

the formulation, while parabens were eliminated because no longer necessary.

The resulting formulation had the composition:

**Parent Formulation**

| Ingredient | % weight/volume |
|---|---|
| Budesonide | 0.018-0.022 |
| Polysorbate | 0.0018-0.0022 |
| Sorbitol solution (70% volume) | 40.9-49.9 |
| Disodium edetate (EDTA) | 0.009-0.011 |
| Avicel RC-591* | 1.08-1.32 |
| Polyvinylpyrrolidone PVP K90 | 9.0-11.0 |
| Potassium sorbate | 0.18-0.22 |
| Sodium citrate dihydrate | 0.0045-0.0055 |
| Citric acid monohydrate | *q.s.* to pH 4.5 |
| Highly purified water | *q.s.* to 100 ml |

*Microcrystalline cellulose and carboxymethylcellulose

Three pilot ballot batches of this formulation were thus manufactured, filled in 100 ml amber glass bottles and put under a formal ICH stability programme. The interim results of the accelerated and the long term stability testing were highly satisfactory.

The present invention also envisages a formulation, further including ascorbic acid because of its anti-oxidative activity:

**Additional formulation *(a)***

| **Ingredient** | **% weight/volume** |
|---|---|
| Budesonide | 0.018-0.022 |
| Polysorbate | 0.0018-0.0022 |
| Sorbitol solution (70% volume) | 40.9-49.9 |
| Disodium edetate EDTA | 0.009-0.011 |
| Avicel RC-591 | 1.08-1.32 |
| Polyvinylpyrrolidone PVP K90 | 9.0-11.0 |
| Potassium sorbate | 0.18-0.22 |
| Sodium citrate dihydrate | 0.0045-0.0055 |
| Ascorbic acid | 0.09-0.11 |
| Citric acid monohydrate | *q.s.* to pH 4.5 |
| Highly purified water | *q.s.* to 100 ml |

The present invention also envisages a formulation, where sorbitol is replaced by ascorbic acid and sucrose:

**Formulation *(b)***

| **Ingredient** | **%weight-volume** |
|---|---|
| Budesonide | 0.018-0.022 |
| Polysorbate | 0.0018-0.0022 |
| Sucrose | 28.62-34.36 |
| Disodium edetate (EDTA) | 0.009-0.011 |
| Avicel RC-591 | 1.08-1.32 |

| | |
|---|---|
| Polyvinylpyrrolidone PVP K90 | 9.0-11.0 |
| Potassium sorbate | 0.18-022 |
| Sodium citrate dihydrate | 0.0045-0.0055 |
| Ascorbic acid | 0.09-0.11 |
| Citric acid monohydrate | *q.s.* to pH 4.5 |
| Highly purified water | *q.s.* to 100 ml |

The present invention also envisages a formulation where ascorbic acid and xylitol replace sorbitol:

**Formulation *(c)***

| **Ingredient** | **%weight-volume** |
|---|---|
| Budesonide | 0.018-0.022 |
| Polysorbate | 0.0018-0.0022 |
| Disodium edetate (EDTA) | 0.009-0.011 |
| Xylitol | 28.62-34.36 |
| Avicel RC-591 | 1.08-1.32 |
| Polyvinylpyrrolidone PVP K90 | 9.0-11.0 |
| Potassium sorbate | 0.18-022 |
| Sodium citrate dihydrate | 0.0045-0.0055 |
| Ascorbic acid | 0.09-0.11 |
| Citric acid monohydrate | *q.s.* to pH 4.5 |
| Highly purified water | *q.s.* to 100 ml |

Pilot batches of Formulation *(a)*, *(b)* and *(c)* were manufactured in 100 ml amber glass bottles and put under stability investigation according to ICH recom-

mended conditions. All above formulations appear to be stable and suitable for clinical investigation.

Specific ways of formulating and carrying out this invention have been disclosed, but it is to be understood that the scope of protection thereof is only restricted by the appended claims.

CLAIMS:

1. A formulation of a stable budesonide high-viscosity oral anti-inflammatory suspension, having the composition:

| **Ingredient** | **% weight/volume** |
|---|---|
| Budesonide | 0.018-0.022 |
| Polysorbate | 0.0018-0.0022 |
| Sorbitol solution (70% volume) | 40.9-49.9 |
| Disodium edetate (EDTA) | 0.009-0.011 |
| Avicel RC-591* | 1.08-1.32 |
| Polyvinylpyrrolidone PVP K90 | 9.0-11.0 |
| Potassium sorbate | 0.18-0.22 |
| Sodium citrate dihydrate | 0.0045-0.0055 |
| Citric acid monohydrate | *q.s.* to pH 4.5 |
| Highly purified water | *q.s.* to 100 ml |

to treat eosiniphilic esophagitis.

2. A formulation of a stable budesonide high-viscosity oral anti-inflammatory suspension, having the composition:

| **Ingredient** | **% weight/volume** |
|---|---|
| Budesonide | 0.018-0.022 |
| Polysorbate | 0.0018-0.0022 |
| Sorbitol solution (70% volume) | 40.9-49.9 |

| | |
|---|---|
| Disodium edetate EDTA | 0.009-0.011 |
| Avicel RC-591 | 1.08-1.32 |
| Polyvinylpyrrolidone (PVP K90) | 9.0-11.0 |
| Potassium sorbate | 0.18-0.22 |
| Sodium citrate dihydrate | 0.0045-0.0055 |
| Ascorbic acid | 0.09-0.11 |
| Citric acid monohydrate | *q.s.* to pH 4.5 |
| Highly purified water | *q.s.* to 100 ml |

to treat eosiniphilic esophagitis.

3. A formulation of a stable budesonide high-viscosity oral anti-inflammatory suspension, having the composition:

| **Ingredient** | **%weight-volume** |
|---|---|
| Budesonide | 0.018-0.022 |
| Polysorbate | 0.0018-0.0022 |
| Sucrose | 28.62-34.36 |
| Disodium edetate (EDTA) | 0.009-0.011 |
| Avicel RC-591 | 1.08-1.32 |
| Polyvinylpyrrolidone (PVP) K90 | 9.0-11.0 |
| Potassium sorbate | 0.18-022 |
| Sodium citrate dihydrate | 0.0045-0.0055 |
| Ascorbic acid | 0.09-0.11 |
| Citric acid monohydrate | *q.s.* to pH 4.5 |

| | |
|---|---|
| Highly purified water | *q.s.* to 100 ml |

to treat eosiniphilic esophagitis.

4. A formulation of a stable budesonide high-viscosity oral anti-inflammatory suspension, having the composition:

| **Ingredient** | **%weight-volume** |
|---|---|
| Budesonide | 0.018-0.022 |
| Polysorbate | 0.0018-0.0022 |
| Disodium edetate (EDTA) | 0.009-0.011 |
| Xylitol | 28.62-34.36 |
| Avicel RC-591 | 1.08-1.32 |
| Polyvinylpyrrolidone PVP K90 | 9.0-11.0 |
| Potassium sorbate | 0.18-022 |
| Sodium citrate dihydrate | 0.0045-0.0055 |
| Ascorbic acid | 0.09-0.11 |
| Citric acid monohydrate | *q.s.* to pH 4.5 |
| Highly purified water | *q.s.* to 100 ml |

to treat eosiniphilic esophagitis.

AMENDED CLAIMS
received by the International Bureau on 31 March 2014 (31.03.2014)

1. A formulation of a stable budesonide high-viscosity oral anti-inflammatory suspension, having the composition:

| **Ingredient** | **% weight/volume** |
|---|---|
| Budesonide | 0.018-0.022 |
| Polysorbate | 0.0018-0.0022 |
| Sorbitol solution (70% volume) | 40.9-49.9 |
| Disodium edetate (EDTA) | 0.009-0.011 |
| Avicel RC-591 | 1.08-1.32 |
| Polyvinylpyrrolidone PVP K90 | 9.0-11.0 |
| Potassium sorbate | 0.18-0.22 |
| Sodium citrate dihydrate | 0.0045-0.0055 |
| Citric acid monohydrate | *q.s.* to pH 4.5 |
| Highly purified water | *q.s.* to 100 ml |

suitable for the treatment of eosiniphilic esophagitis.

2. A formulation of a stable budesonide high-viscosity oral anti-inflammatory suspension according to Claim 1, further including:

| **Ingredient** | **% weight/volume** |
|---|---|
| Ascorbic acid | 0.09-0.11 |

suitable for the treatment of eosiniphilic esophagitis.

3. A formulation of a stable budesonide high-

viscosity oral anti-inflammatory suspension, having the composition:

| **Ingredient** | **%weight-volume** |
|---|---|
| Budesonide | 0.018-0.022 |
| Polysorbate | 0.0018-0.0022 |
| Sucrose | 28.62-34.36 |
| Disodium edetate (EDTA) | 0.009-0.011 |
| Avicel RC-591 | 1.08-1.32 |
| Polyvinylpyrrolidone (PVP) K90 | 9.0-11.0 |
| Potassium sorbate | 0.18-022 |
| Sodium citrate dihydrate | 0.0045-0.0055 |
| Ascorbic acid | 0.09-0.11 |
| Citric acid monohydrate | *q.s.* to pH 4.5 |
| Highly purified water | *q.s.* to 100 ml |

suitable for the treatment of eosiniphilic esophagitis.

4. A formulation of a stable budesonide high-viscosity oral anti-inflammatory suspension, having the composition:

| **Ingredient** | **%weight-volume** |
|---|---|
| Budesonide | 0.018-0.022 |
| Polysorbate | 0.0018-0.0022 |
| Disodium edetate (EDTA) | 0.009-0.011 |
| Xylitol | 28.62-34.36 |

| | |
|---|---|
| Avicel RC-591 | 1.08-1.32 |
| Polyvinylpyrrolidone PVP K90 | 9.0-11.0 |
| Potassium sorbate | 0.18-022 |
| Sodium citrate dihydrate | 0.0045-0.0055 |
| Ascorbic acid | 0.09-0.11 |
| Citric acid monohydrate | *q.s.* to pH 4.5 |
| Highly purified water | *q.s.* to 100 ml |

suitable for the treatment of eosiniphilic esophagitis.

STATEMENT

UNDER ART. 19 PCT

Claims 1 to 4 as amended now recite formulations of a stable budesonide high-viscosity oral anti-inflammatory suspension **suitable** for the treatment of eosiniphilic esophagitis. The impact of such amendment is that the claims now unambiguously recite formulations suitable for use in a medical treatment (as proven in the description), not *uses* of a formulation in a medical treatment.

# INTERNATIONAL SEARCH REPORT

International application No
PCT/IT2013/000096

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K9/06 A61K9/14 A61K31/58
ADD.

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

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 practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 14 November 2013 | 22/11/2013 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Laurent, Antoine |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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