Inventive step

Juxtaposition vs Synergistic Effects

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The Industrial Property Law establish:

**Novel:**

Anything not found in the prior art.

**Inventive Step:**

Creative process where the results of which are not obvious from the prior art to a person skilled in the art.

**Industrial Application:**

Possibility that an invention has practical utility or can be made or used in any branch of economic activity.

The person skilled in the art is considered to be someone who possesses general knowledge and skills within the considered technical field.
Subparagraph VIII of the Article 19 of the Industrial Property Law provide that is not considered an invention:

Juxtaposition of known inventions or mixtures of known products, except where as to produce a result that is not obvious to a person skilled in the art.
Example 1

A pharmaceutical formulation comprising loratadine and a leukotriene antagonist and its use in the treatment of specific diseases

(MX 9806421, EP 1 014 972 A1)
ANTECEDENTES DE LA INVENCION

Loratadina es un antihistamínico con propiedades de H-receptor antagonista útil en el tratamiento de alergias y está descrita en la patente de E.U.A. 4.2282.233.

Se sabe que los antagonistas de leucotrieno son útiles en el tratamiento de asma, reacciones alérgicas e inflamación.

Ahora con esta invención, se provee un método de tratamiento de asma, alergia e inflamación con una combinación de estos dos agentes que es más eficiente que el agente mismo.

BREVE DESCRIPCION DE LA INVENCION

Esta invención se refiere a un método de tratamiento de asma, alergia e inflamación mediante la administración de una cantidad efectiva de loratadina y una cantidad efectiva de un antagonista de leucotrieno ya sea mediante esencialmente la
The combination of loratadine and a leukotriene antagonist that is provided is useful in the treatment of asthma, allergic reactions and inflammation.

The leukotriene antagonist is motelukast-sodium.

The combination of these two agents is more efficacious than either by itself.

It is not described in which form the combination is more efficacious.
Claims

1. A pharmaceutical formulation comprising as active ingredients loratadine, montelukast-sodium and a pharmaceutically acceptable carrier.

2. The use of an effective amount of loratadine and an effective amount of montelukast-sodium for preparing a medicament for treatment of asthma, allergic reactions and inflammation.
D1: Loratadine is an antihistamine with $H_1$-receptor antagonist properties useful in the treatment of allergies. (US 4 282 233)

D2: Montelukast sodium, a leukotriene antagonist, is known to be useful in the treatment of asthma, allergic reactions and inflammation. This compound can be advantageously combined with $H_1$ or $H_2$-receptor antagonist. (EP 0 480 717)
Analysis

Closest prior art documents: D1 and D2

Differences between the invention and the closest prior art:

Loratadine and montelukast sodium are combined.

The pharmaceutical formulation is NEW

Effects of the difference:

A pharmaceutical formulation more efficacious for treating asthma, allergic reactions and inflammation.
D2 teaches that it is possible to get advantageous combinations of the leukotriene antagonists described with H₁-receptor antagonists. (Loratadine).

The description point out that the combination of both agents is more efficacious (synergistic effects?), however data showing greater efficacy are not provided.

The combination of both agents has the same utility than either by itself: is useful for treating asthma, allergies and inflammation and there is no an unexpected effect.

The combination is obvious.
The pharmaceutical formulation comprising loratadine and montelukast-sodium is new, but has no inventive step.

This combination is a juxtaposition of inventions.
Example 2

Synergistic combination comprising roflumilast and an anticholinergic agent selected from ipratropium, oxitropium and tiotropium salts for the treatment of respiratory diseases

(MX 256 201, EP 1 610 787 B1)
Pharmaceutical composition suited for administration by inhalation for treating a respiratory disease, comprising an effective amount of roflumilast (a PDE4 inhibitor), an effective amount of an anticholinergic agent selected from the group of ipratropium, oxtropium and tiotropium salts, together with pharmaceutically acceptable excipients and/or carriers.

The two active compounds act together in a synergistic manner.

Respiratory diseases mentioned are bronchitis, obstructive bronchitis, allergic bronchitis, allergic asthma, bronchial asthma and Chronic Obstructive Pulmonary Disease.
Pharmacological data:

- A study on the effects of roflumilast in combination with tiotropium-bromide in the inhibition of methacholine-induced bronchoconstriction in Guinea Pigs was presented.

- Injection of methacholine induced an immediate bronchoconstriction characterized by a decrease of dynamic lung compliance (COM) and airway conductance (CON).

- Once administered the compounds (roflumilast, tiotropium-bromide and the combination of both) under the conditions described there, COM and CON were determined.
Results:

- Treatment with roflumilast had no significant effect on methacholine-induced bronchospasm.

- Treatment with tiotropium-bromide had no significant effect on methacholine-induced bronchospasm.

- Combination of both agents lead to a synergistic inhibition of COM decrease and CON decrease.
Figure 1

Methacholine-induced Compliance Decrease in Guinea Pigs

![Graph showing compliance vs. time for different treatments.](image1)

Data are shown as mean ± SEM. *p<0.05, **p<0.01 vs. placebo.

Figure 2

Methacholine-induced Conductance Decrease in Guinea Pigs

![Graph showing conductance vs. time for different treatments.](image2)

Data are shown as mean ± SEM. *p<0.05, **p<0.01 vs. placebo.
**Figures**

**Figure 3**

AUC Compliance 0-120 s

<table>
<thead>
<tr>
<th>Inhibition</th>
<th>Placebo n=10</th>
<th>Roflumilast 4 mg/kg i.t. n=6</th>
<th>Tiotropium 1 µg/kg i.v. n=7</th>
<th>Roflumilast + Tiotropium n=6</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1.6 %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.0 %</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>41.1 %</td>
<td></td>
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</tr>
</tbody>
</table>

Data are shown as mean ± SEM. **p<0.01 vs. placebo.**

**Figure 4**

AUC Conductance 0 - 120 s

<table>
<thead>
<tr>
<th>Inhibition</th>
<th>Placebo n=10</th>
<th>Roflumilast 4 mg/kg i.t. n=6</th>
<th>Tiotropium 1 µg/kg i.v. n=7</th>
<th>Roflumilast + Tiotropium n=6</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.6 %</td>
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<td></td>
</tr>
<tr>
<td>5.9 %</td>
<td></td>
<td></td>
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<tr>
<td>25.0 %</td>
<td></td>
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</tbody>
</table>

Data are shown as mean ± SEM. *p<0.05 vs. placebo.
1. Pharmaceutical composition suited for administration by inhalation, which comprises roflumilast and an anticholinergic agent selected from the group of ipratropium, oxitropium and tiotropium salts together with pharmaceutically acceptable excipients and/or carriers.
**Prior art**

<table>
<thead>
<tr>
<th>D1: Combination of a compound from the class of PDE4 inhibitors with a compound from the class of anticholinergic agents for the treatment of the respiratory tract disorders. (WO 02/069945)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D2: Combination of a compound from the class of PDE4 inhibitors with a compound from the class of anticholinergic agents for the treatment of the respiratory tract disorders. (WO 03/011274)</td>
</tr>
<tr>
<td>D3: Combination of PDE4 inhibitor together with tiotropium and derivatives thereof for the treatment of respiratory diseases. (WO 02/096423)</td>
</tr>
</tbody>
</table>
Differences between the invention and the closest prior art:

Specific combination of roflumilast and an anticholinergic agent selected from the group of ipratropium, oxtropium and tiotropium salts.

The pharmaceutical composition is new

Effect of the difference:

A synergistic pharmaceutical composition for the treatment of respiratory diseases.
In the description were presented data from a study of inhibition of methacholine-induced bronchoconstriction, where only the combination of roflumilast and tiotropium-bromide was tested.

The results showed a synergistic effect in the inhibition of the bronchoconstriction by said combination.

The synergistic effect shown is considered a non obvious result.
The other possible combinations were not tested.

In the absence of evidence for the other possible combinations, only was recognized the inventive step for the combination of roflumilast and tiotropium-bromide.
The pharmaceutical composition suited for administration by inhalation, which comprises roflumilast and tiotropium-bromide is new and inventive.
Thank you!

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