



## Inventive step

# Juxtaposition vs Synergistic Effects

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# Patentability requirements

**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.**



## Non-inventions

**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)**





## Description

### 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





## Description

- 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.**





## Prior art

- D1:** Loratadine is an antihistamine with H<sub>1</sub>-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<sub>1</sub> or H<sub>2</sub>-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.





## Analysis

- ➔ D2 teaches that is possible to get advantageous combinations of the leukotriene antagonists described with H<sub>1</sub>-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.





## Conclusion

- ➔ 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)**





## Description

- 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, oxitropium 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.

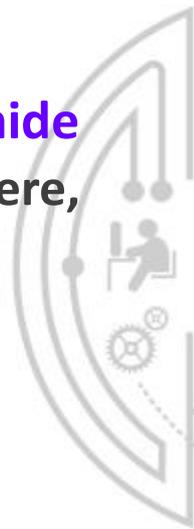




## Description

### 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.





## Description

### 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.

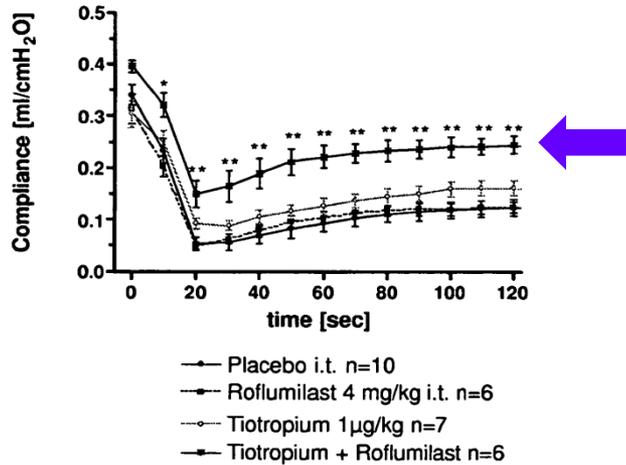




# Figures

**Figure 1**

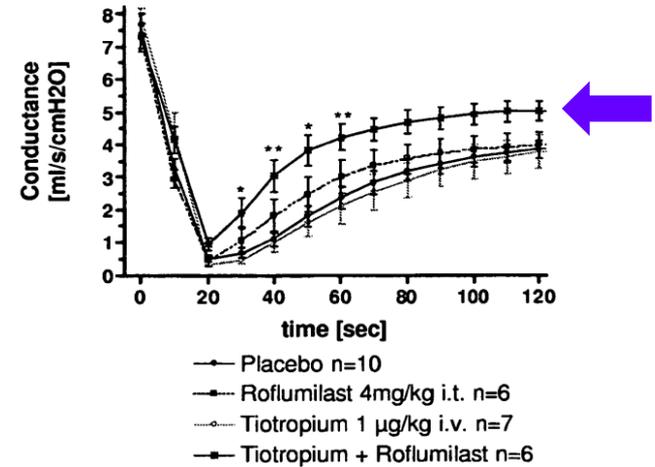
## Methacholine-induced Compliance Decrease in Guinea Pigs



Data are shown as mean  $\pm$  SEM. \* $p$ <0.05, \*\* $p$ <0.01 vs. placebo

**Figure 2**

## Methacholine-induced Conductance Decrease in Guinea Pigs



Data are shown as mean  $\pm$  SEM. \* $p$ <0.05, \*\* $p$ <0.01 vs. placebo



# Figures

Figure 3

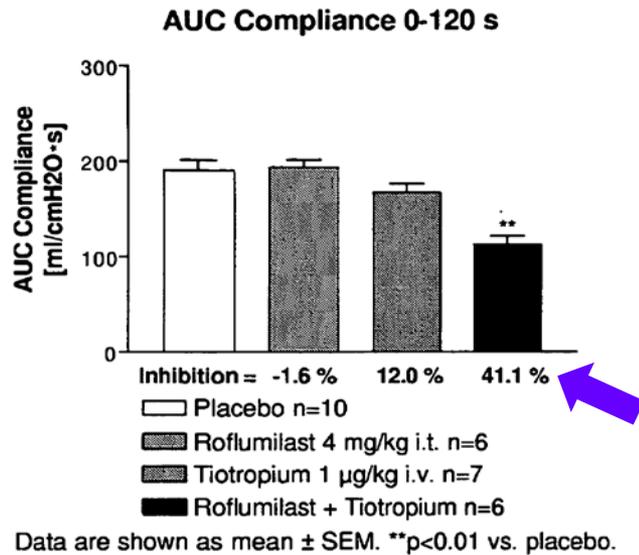
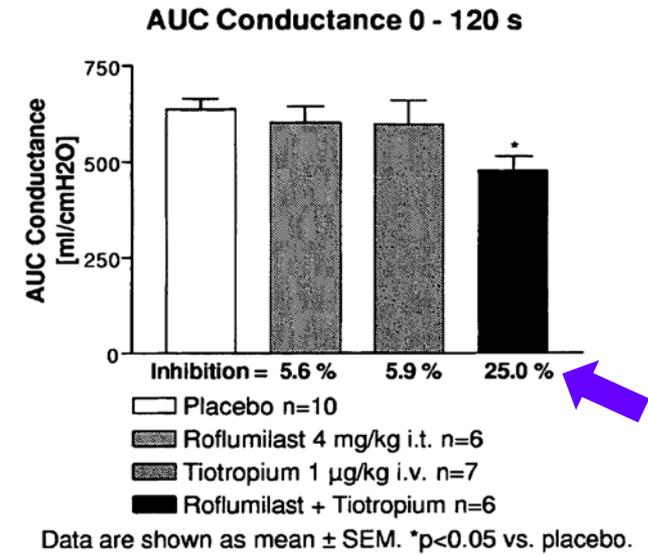


Figure 4





## Claims

- 1. Pharmaceutical composition suited for administration by inhalation, which comprises roflumilast and a anticholinergic agent selected from the group of ipratropium, oxitropium and tiotropium salts together with pharmaceutically acceptable excipients and/or carriers.**





## Prior art

- 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)**
- 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)**
- D3:**      **Combination of PDE4 inhibitor together with tiotropium and derivatives thereof for the treatment of respiratory diseases. (WO 02/096423)**



## Analysis

Closest prior art document: D3

Differences between the invention and the closest prior art:

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



**The pharmaceutical composition is new**

Effect of the difference:

A **synergistic** pharmaceutical composition for the treatment of respiratory diseases.





## Analysis

- ➔ 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.





## Analysis

- ➔ 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**.





## Conclusion

- ➔ The pharmaceutical composition suited for administration by inhalation, which comprises roflumilast and tiotropium-bromide **is new and inventive.**





# Thank you!

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