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(54) Title:
ORAL COMPOSITIONS CONTAINING BROMOCHLOROPHENE AND ZINC IONS

(57) Abstract

Oral compositions for use in oral hygiene comprise both bromochlorophene and zinc ions in a weight:weight ratio of from 1:0.1 to 1:50. The combination of these components provides a synergistic anti-plaque effect in use. The compositions may take the form of, for example, a dentifrice, mouthwash, toothpowder, chewing gum or lozenge.
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TD Chad  
TG Togo  
US United States of America
ORAL COMPOSITIONS CONTAINING BROMOCHLOROPHEN AND ZINC IONS

The present invention relates to oral compositions which comprise at least two active ingredients selected from agents which decrease the sensitivity of teeth, anti-plaque agents and anti-tartar agents. Beneficial effects are obtained by combining two or more active ingredients within a single composition.

Oral compositions containing anti-plaque agents are well known to those skilled in the art. Typical anti-plaque agents include cationic antibacterial materials such as chlorhexidine and non-cationic compounds such as phenol derivatives. Preferred anti-plaque agents are non-cationic compounds, for example, bromochlorophene, triclosan, hexachlorophene and dichlorophene.

Anti-tartar agents are also well known and include zinc salts such as zinc citrate (also known to have anti-plaque activity) and various polyphosphates.

Surprisingly, the applicants have found an entirely unexpected advantage may be obtained by combining the known active ingredients bromochlorophene and zinc ions within a single oral health composition. Combinations of active ingredients are known in the art, see for example EP-161899 which discloses toothpaste compositions containing triclosan and zinc citrate. However, the applicants have found that specific combinations of bromochlorophene and zinc ions provide a synergistic anti-plaque effect which is not provided by the prior art compositions.

Thus the present invention provides oral compositions which comprise bromochlorophene and zinc ions in a weight:weight ratio in the range of 1:0.1 to 1:50, preferably 1:1 to 1:10, more preferably 1:1.3 to
1:8, preferably 1:1.5 to 1:8. The bromochlorophene generally comprises 0.002 to 2%, preferably 0.01 to 2%, preferably 0.01 to 0.5%, suitably 0.05 to 0.2%, preferably about 0.1% by weight of the composition. Zinc ions generally comprise 0.0005 to 0.2%, preferably 0.02 to 2% preferably 0.1 to 1%, preferably about 0.155% by weight of the composition.

Zinc ions are generally provided in the form of pharmaceutically acceptable zinc salts such as zinc citrate, zinc chloride, zinc sulphate, zinc acetate, zinc lactate, zinc salicylate, zinc thiocyanate, zinc glucoheptanoate, zinc gluconate, zinc maleate, zinc fumarate or mixtures thereof. Preferably zinc ions are provided in the form of zinc citrate which may comprise 0.05 to 4%, preferably 0.2 to 4%, most preferably 0.3 to 3% by weight of the composition.

The oral composition may be in the form of, for example, a dentifrice, mouthwash, toothpowder, chewing gum, lozenge, denture cleanser or toothbrush sanitiser. Such compositions may contain conventional base materials such as, for example, humectants, surfactants, emulsifiers, gelling agents e.g. cellulose gum, xanthan gum, hydroxyethyl cellulose, carrageenan and alginates, and abrasives and may be formulated in a known manner. Further optional ingredients may be added if desired, for example, fluoride salts, flavourings, colourings, sweeteners, preservatives and alcohol.

It is often desirable to add a fluoride-containing substance, such as sodium monofluorophosphate, sodium fluoride, or an organic amine fluoride. Such components are typically added in amounts of between 0.01% and 5% by weight of the composition. For example, sodium monofluorophosphate may suitably be included in a dentifrice formulation in an amount of about 1% by weight, and sodium fluoride may be included in a
mouthwash formulation in an amount of about 0.05% by weight.

The concentrations of bromochloropheine and zinc citrate may be varied within the limits described above as appropriate to the particular type of formulation prepared. For example, as a result of the relatively low solubility of bromochloropheine in water, mouthwash formulations will typically contain bromochloropheine at concentrations about ten times lower than those used in toothpastes/dentifrices.

The oral compositions according to the invention may also contain conventional ingredients which decrease the sensitivity of teeth. These ingredients are usually included to between 1 and 15% by weight of the composition and include, for example, potassium salts such as potassium citrate, potassium chloride and potassium nitrate, strontium salts such as strontium chloride and strontium acetate, and formaldehyde. For example, strontium chloride may comprise 5 to 15%, suitably about 10% by weight of the composition whilst potassium nitrate may comprise 2 to 10%, suitably about 5% by weight, and formaldehyde may comprise 0.5 to 5%, suitably about 1.3% by weight of the composition.

Preferred compositions according to the invention are dentifrices which further comprise a dentally acceptable abrasive. Typical dentally acceptable abrasives include alumina, silica, synthetic resins and mixtures thereof. Preferred compositions contain one or more silica blends having abrasive and/or thickening properties. Preferred abrasives are non-crystalline silica abrasives, particularly in the form of precipitated silica or milled silica gels available commercially for example under the trade names Zeodont (Zeofinn OY) and Syloblanc (Grace) respectively. Preferred dentifrice compositions according to the
invention comprise 5% to 50%, more preferably 15% to 30% by weight of silica.

The anti-plaque activity of the compositions according to the present invention has been demonstrated as follows. Thin strips of aluminium were used as "artificial tooth" surfaces on which plaque, collected from a small number of donors, was grown. Growth was encouraged by the provision of conditions resembling a normal oral environment (saliva, nutrients, pH and temperature) over a two day period with simulations made of the intake of two meals and of a sleeping, low nutrient period. The aluminium strips (and plaque) were exposed for one minute on two occasions to a solution of the composition to be tested with distilled water and fresh saliva, thus simulating evening and morning toothbrushing sessions. Following the second exposure, plaque remaining on the strips after a four hour growth period and subsequent rinsing was dispersed by ultrasonic vibration. The optical density of the resulting plaque suspensions at 570 nm (two replicate readings per strip) were used to estimate the percentage reduction in plaque growth compared to plaque growth on test strips exposed to a control composition of saliva and water.

Typical compositions are illustrated in Examples 1 to 6 hereinafter.

**Toothpaste base formulation**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>% w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sorbitol (70% solution)</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>Sodium monofluorophosphate</td>
<td>0.84</td>
</tr>
<tr>
<td>3</td>
<td>Sodium lauryl sulphate (sold under the trade name Empicol LZ)</td>
<td>1.5</td>
</tr>
<tr>
<td>4</td>
<td>Titanium dioxide (sold under the trade designation PH EUR)</td>
<td>0.75</td>
</tr>
<tr>
<td>5</td>
<td>Sodium saccharin BP</td>
<td>0.26</td>
</tr>
</tbody>
</table>
6) Silica (sold under the trade name Zeodent 113)  12.22

7) Silica (sold under the trade name Zeodent 163)  8.33

8) Sodium carboxymethylcellulose (sold under the trade name Wacocel CRT 2000 PA)  0.9

9) Flavouring  1.0 v

10) Water  ad. 100

1. Sorbitol solution (component 1) and water were mixed together.

2. Components 2 and 5 were added and the mixture stirred until dissolved.

3. Components 3, 4, 6, 7 and 8 were added and the mixture was mixed thoroughly under vacuum until a smooth paste was formed.

4. Flavouring (component 9) was mixed in under vacuum and the composition was deaerated to give the toothpaste base formulation.

Example 1

The base formulation was made up containing 0.1% w/w bromochlorophene (dissolved in flavouring and added at Stage 4) and 0.5% w/w zinc citrate trihydrate (added at Stage 3) to give the toothpaste of Example 1.
Example 2

The base formulation was made up containing 0.1% w/w bromochlorophene (dissolved in flavouring and added at Stage 4) and 2.0% w/w zinc citrate trihydrate (added at Stage 3) to give the toothpaste of Example 2.

Study 1

The anti-plaque activity of the formulations of Examples 1 and 2 were compared to those of the base formulation containing 0.1% w/w bromochlorophene alone and to a proprietary brand of toothpaste containing 0.2% triclosan and 0.5% zinc citrate.

Study 1 employed six aluminium strips for each treatment group and two absorbance readings were taken per sample. The percentage reduction in amount of plaque present compared to the control (saliva and water) are shown in Table 1. Non-parametric Kruskal-Wallis analysis of variance, followed by Miller's Multiple Comparison technique, shows there was a statistically significant reduction in plaque level on strips treated with the toothpaste of Examples 1 and 2, containing 0.1% bromochlorophene and 0.5% zinc citrate and 0.1% bromochlorophene and 2% zinc citrate respectively, when compared to the control. There was no statistically significant difference between plaque level on control strips and plaque level on strips exposed to toothpastes containing either 0.1% bromochlorophene or 0.2% triclosan and 0.5% zinc citrate.
Table 1

<table>
<thead>
<tr>
<th>Sample</th>
<th>% Reduction in plaque growth</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toothpaste base + 0.1% bromochlorophene</td>
<td>41</td>
<td>No</td>
</tr>
<tr>
<td>Proprietary brand toothpaste containing 0.2% triclosan + 0.5% zinc citrate</td>
<td>36</td>
<td>No</td>
</tr>
<tr>
<td>Toothpaste base + 0.1% bromochlorophene + 0.5% zinc citrate (Example 1)</td>
<td>86</td>
<td>Yes p &lt; 0.05</td>
</tr>
<tr>
<td>Toothpaste base + 0.1% bromochlorophene + 2.0% zinc citrate (Example 2)</td>
<td>82</td>
<td>Yes p &lt; 0.05</td>
</tr>
</tbody>
</table>

Study 2

The anti-plaque activity of the formulation of Example 1 was compared to those of the base formulation containing 0.1% bromochlorophene alone or containing 0.2% triclosan (dissolved in flavouring and added at Stage 4) and 0.5% zinc citrate.

Study 2 employed ten aluminium strips for each treatment group. The percentage reduction in amount of plaque present compared to the control (saliva and water) are shown in Table 2. Bartlett’s test for homogeneity of variances between groups indicated that parametric analysis of the results obtained was justified. Parametric one-way analysis of variance, followed by a Tukey Multiple Range test, shows there was a statistically significant reduction in plaque levels on strips treated with the toothpaste of Example 1, containing 0.1% bromochlorophene and 0.5% zinc citrate, when compared to the control. There was no statistically significant difference between plaque
level on control strips and plaque level on strips exposed to toothpastes containing either 0.1% bromochlorophene or 0.2% triclosan and 0.5% zinc citrate.

5 Table 2

<table>
<thead>
<tr>
<th>Sample</th>
<th>% Reduction in plaque growth</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toothpaste base + 0.1% bromochlorophene</td>
<td>28</td>
<td>No</td>
</tr>
<tr>
<td>Toothpaste base + 0.1% bromochlorophene + 0.5% zinc citrate (Example 1)</td>
<td>48</td>
<td>Yes p &lt;0.05</td>
</tr>
<tr>
<td>Toothpaste base + 0.2% triclosan + 0.5% zinc citrate</td>
<td>30</td>
<td>No</td>
</tr>
</tbody>
</table>

15 Study 3

The antiplaque activity of the formulation of Example 1 was compared to those of the base formulation containing 0.1% bromochlorophene alone or containing 0.5% zinc citrate.

20 Study 3 employed six aluminium strips for each treatment group. The percentage reduction in amount of plaque present compared to the control (saliva and water) are shown in Table 3. Non-parametric Kruskal-Wallis analysis of variance, followed by Miller's Multiple Comparison technique, shows there was a statistically significant reduction in plaque level on strips treated with the toothpaste of Example 1, containing 0.1% bromochlorophene and 0.5% zinc citrate, and a toothpaste comprising the toothpaste base and 0.1% bromochlorophene alone. There was no significant difference between plaque level on control strips and
plaque level on strips exposed to toothpaste containing 0.5% zinc citrate.

Table 3

<table>
<thead>
<tr>
<th>Sample</th>
<th>% Reduction in plaque growth</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toothpaste base + 0.1% bromochlorophene</td>
<td>73.5</td>
<td>Yes p &lt;0.05</td>
</tr>
<tr>
<td>Toothpaste base + 0.5% zinc citrate</td>
<td>69.8</td>
<td>No</td>
</tr>
<tr>
<td>Toothpaste base + 0.1% bromochlorophene + 0.5% zinc citrate (Example 1)</td>
<td>80.8</td>
<td>Yes p &lt;0.05</td>
</tr>
</tbody>
</table>

Examples 3 and 4

Toothpastes are prepared in conventional manner having the following formulations:

<table>
<thead>
<tr>
<th>15</th>
<th></th>
<th>Ex. 3</th>
<th>Ex. 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% w/w</td>
<td>% w/w</td>
<td></td>
</tr>
<tr>
<td>Sorbitol (70% solution)</td>
<td>40</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Potassium Nitrate</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Sodium Monofluorophosphate</td>
<td>0.8</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Silica</td>
<td>22</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Sodium Lauryl Sulphate</td>
<td>1.5</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Zinc citrate trihydrate</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Titanium Dioxide</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Sodium Methyl Cocoyl Taurate</td>
<td>0.5</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>Bromochlorophene</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Cellulose Gum</td>
<td>1.1</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Preservative</td>
<td>0.1</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Flavour &amp; Saccharin</td>
<td>1.2</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Colour</td>
<td>q.s.</td>
<td>q.s.</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>Water</td>
<td>to 100</td>
<td>to 100</td>
</tr>
</tbody>
</table>
Examples 5 and 6

Toothpastes are prepared in conventional manner having the following formulations:

<table>
<thead>
<tr>
<th>5</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorbitol (70% solution)</td>
<td>40</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium Monofluorophosphate</td>
<td>0.8</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silica</td>
<td>22</td>
<td>22.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium Lauryl Sulphate</td>
<td>1.5</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Zinc citrate trihydrate</td>
<td>0.5</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Titanium Dioxide</td>
<td>1</td>
<td>0.96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium Methyl Cocomyl Taurate</td>
<td>0.5</td>
<td>1.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bromochlorophene</td>
<td>0.1</td>
<td>0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellulose Gum</td>
<td>1</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Preservative</td>
<td>0.1</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Flavour &amp; Saccharin</td>
<td>1.2</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colour</td>
<td>q.s.</td>
<td>q.s.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyethylene glycol 400</td>
<td>-</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strontium chloride hexahydrate</td>
<td>-</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Water</td>
<td>to 100</td>
<td>to 100</td>
<td></td>
</tr>
</tbody>
</table>

Example 7

The base formulation was made up containing 9.44% w/w silica (sold under the trade name Zeodent 113) to give the toothpaste of Example 7.

Example 8

A mouthwash was prepared in conventional manner having the following formulation:
Hydroxyethylcellulose (sold under the trade name Natrosol 250 HR) 0.20
Dehydrated alcohol BP 8.50
Flavour 0.15
Polysorbate 20 (sold under the trade name Tween 20) 0.15
Polyethylene glycol - 40 Hydrogenated castor oil (sold under the trade name Croduret 40) 0.15
Sodium saccharin BP 0.04
Sodium fluoride 0.05
Glycerin BP 4.00
Bromochlorophene 0.02
Zinc citrate trihydrate 0.1
Sodium lauryl sulphate 0.75
Sorbitol (70% solution) 11.00
Polyethylene glycol - 400 5.00
Propylene glycol 5.00
Purified water BP to 100

Example 9

A toothpaste was prepared in conventional manner having the following formulation:

<table>
<thead>
<tr>
<th>% w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorbitol (70% solution) 50</td>
</tr>
<tr>
<td>Sodium monofluorophosphate 0.84</td>
</tr>
<tr>
<td>Silica 21.66</td>
</tr>
<tr>
<td>Sodium lauryl sulphate 1.5</td>
</tr>
<tr>
<td>Sodium hydroxide BP 0.2</td>
</tr>
<tr>
<td>Zinc citrate trihydrate 0.5</td>
</tr>
<tr>
<td>Titanium dioxide PH EUR 0.75</td>
</tr>
<tr>
<td>Bromochlorophene 0.1</td>
</tr>
<tr>
<td>Sodium carboxymethylcellulose 0.9</td>
</tr>
<tr>
<td>Flavour 1.0v</td>
</tr>
<tr>
<td>Sodium saccharin BP 0.26</td>
</tr>
<tr>
<td>Purified water BP to 100</td>
</tr>
</tbody>
</table>
Claims

1. An oral composition comprising bromochlorophene and zinc ions in a weight:weight ratio in the range of 1:0.1 to 1:50.

2. A composition as claimed in Claim 1 wherein the weight:weight ratio of bromochlorophene to zinc ions is 1:1 to 1:10.

3. A composition as claimed in Claim 2 wherein the weight:weight ratio of bromochlorophene to zinc ions is 1:1.3 to 1:8.

4. A composition as claimed in Claim 3 which comprises 0.002 to 2% by weight bromochlorophene.

5. A composition as claimed in Claim 4 which comprises 0.01 to 2% by weight bromochlorophene.

6. A composition as claimed in any one of the preceding claims which comprises 0.005 to 2% by weight zinc ions.

7. A composition as claimed in Claim 6 which comprises 0.02 to 2% by weight zinc ions.

8. A composition as claimed in any one of the preceding claims which comprises zinc citrate.

9. A composition as claimed in Claim 8 which comprises 0.01 to 4% by weight zinc citrate.

10. A composition as claimed in Claim 9 which comprises 0.05 to 4% by weight zinc citrate.
11. A composition as claimed in any one of the preceding claims which comprises an ingredient which decreases the sensitivity of teeth.

12. A composition as claimed in any one of the preceding claims in the form of a dentifrice which comprises a dentally acceptable abrasive.

13. A method of cleansing the mouth for cosmetic purposes by application of a composition as claimed in any one of the preceding claims.

14. A method for prophylaxis or treatment of gum disease or dental caries by application of a composition as claimed in any one of Claims 1 to 12.

15. The use of a composition as claimed in any one of Claims 1 to 12 in the prophylaxis or treatment of gum disease or dental caries.

16. The use of a composition as claimed in any one of Claims 1 to 12 in the manufacture of a medicament for the prophylaxis or treatment of gum disease or dental caries.
I. CLASSIFICATION OF SUBJECT MATTER

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 7/16

II. FIELDS SEARCHED

Minimum Documentation Searched

<table>
<thead>
<tr>
<th>Classification System</th>
<th>Classification Symbols</th>
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<tr>
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<td>A 61 K</td>
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Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched

III. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of Document, 11 with indication, where appropriate, of the relevant passages 12</th>
<th>Relevant to Claim No.13</th>
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<tbody>
<tr>
<td>X</td>
<td>EP,A,0161898 (UNILEVER PLC) 21 November 1985, see pages 1-3; page 10, lines 20-35; page 11, line 35; page 12, lines 30-35; page 13, lines 6-35; page 14; example 4; table 5; claims 1,6,8</td>
<td>1-16</td>
</tr>
</tbody>
</table>

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IV. CERTIFICATION

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Signature of Authorized Officer

MISS T. TAZELAAR

Form PCT/ISA/210 (second sheet) (January 1985)
V. [X] OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claim numbers Authority, namely:
   because they relate to subject matter not required to be searched by this
   Remark: Although claim 14 is directed to a method of
   treatment of the human body, the search has been carried
   out and based on the alleged effects of the composition.

2. □ Claim numbers
   because they relate to parts of the International application that do not comply
   with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. □ Claim numbers
   because they are dependent claims and are not drafted in accordance with
   the second and third sentences of PCT Rule 6.4(a).

VI. [□] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This International Searching Authority found multiple Inventions in this International application as follows:

1. □ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims
   of the International application

2. □ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only
   those claims of the International application for which fees were paid, specifically claims:

3. □ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to
   the invention first mentioned in the claims; it is covered by claim numbers:

4. □ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not
   invite payment of any additional fee.

Remark on Protest:

□ The additional search fees were accompanied by applicant’s protest.
□ No protest accompanied the payment of additional search fees.
This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 22/04/92.
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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For more details about this annex: see Official Journal of the European Patent Office, No. 12/82.