Title: NOVEL CRYSTALLINE FORMS OF ARIPIPRAZOLE

Abstract: The present invention provides novel crystalline forms of aripiprazole and aripiprazole hydrochloride, processes for their preparation and pharmaceutical compositions containing them.
NOVEL CRYSTALLINE FORMS OF ARIPIPRAZOLE

FIELD OF THE INVENTION

The present invention provides novel crystalline forms of aripiprazole and aripiprazole hydrochloride, processes for their preparation and pharmaceutical compositions containing them.

BACKGROUND OF THE INVENTION

Aripiprazole of formula (1):

\[ \text{Structure of Aripiprazole} \]

or 7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-2(1H)-quinolinone and its salts are useful for treating schizophrenia and their therapeutic uses were disclosed in US 5,006,528.

Processes for the preparation of aripiprazole and its salts were described in US 5,006,528. These processes do not produce well defined, reproducible crystalline forms.

Thus there is a need for stable and reproducible crystalline forms of aripiprazole and its salts.

We have discovered two novel crystalline forms of aripiprazole and four novel crystalline forms of aripiprazole hydrochloride. The novel forms have been found to be stable over the time and reproducible and so, suitable for pharmaceutical preparations.

Thus, the object of the present invention is to provide stable novel crystalline forms of aripiprazole, processes for preparation of the novel
crystalline forms and pharmaceutical compositions containing these novel crystalline forms.

Another object of the present invention is to provide stable novel crystalline forms of aripiprazole hydrochloride, processes for preparation of the novel crystalline forms and pharmaceutical compositions containing these novel crystalline forms.

Since the novel crystalline forms of aripiprazole hydrochloride are obtained with high purity, preparation of aripiprazole via the crystalline forms of aripiprazole hydrochloride serves as a means of producing pure aripiprazole.

SUMMARY OF THE INVENTION

According to one aspect of the present invention, there is provided a novel crystalline form of aripiprazole, designated as Form I, characterized by an x-ray powder diffraction pattern having peaks expressed as \( \theta \) at about 8.7, 11.6, 16.3, 17.7, 18.6, 20.3, 23.4, 24.9 degrees. Figure 1 shows typical Form I x-ray powder diffraction pattern.

According to another aspect of the present invention there is provided a process for preparation of the Form I of aripiprazole comprising the steps of:

a) dissolving aripiprazole in a suitable solvent;
b) refluxing for about 30 minutes to 1 hour;
c) cooling slowly to about 15\(^\circ\)C to 25\(^\circ\)C;
d) maintaining for about 2 hour to 4 hours at about 15\(^\circ\)C to 25\(^\circ\)C; and
e) filtering the solid separated.

The suitable solvent is selected from the group consisting of acetone, ethyl acetate, methanol or ethanol.

According to another aspect of the present invention, there is provided a novel crystalline form of aripiprazole, designated as Form II, characterized by an x-ray powder diffraction pattern having peaks expressed as \( \theta \) at about 12.7, 15.1, 17.5, 18.2, 18.8, 19.5, 20.6, 21.2, 22.6, 23.3, 24.2, 24.9, 27.6, 30.0, 31.6, 35.8 degrees. Figure 2 shows typical Form II x-ray powder diffraction pattern.

According to another aspect of the present invention there is provided a process for preparation of the Form II of aripiprazole, which comprises dissolving aripiprazole in tetrahydrofuran and vacuum drying at about 25\(^\circ\)C or spray drying.
According to another aspect of the present invention, there is provided a novel crystalline form of aripiprazole hydrochloride, designated as Form A, characterized by an x-ray powder diffraction pattern having peaks expressed as 2θ at about 6.2, 8.5, 11.5, 15.2, 15.5, 16.8, 17.2, 18.3, 18.9, 19.6, 20.6, 21.3, 23.4, 24.1, 24.7, 25.9, 27.5, 28.3, 28.9, 32.8 degrees. Figure 3 shows typical Form A x-ray powder diffraction pattern.

According to another aspect of the present invention there is provided a process for preparation of the Form A of aripiprazole hydrochloride comprising the steps of:

a) dissolving aripiprazole in methanol or isopropyl alcohol;
b) adding hydrochloric acid;
c) maintaining for about 1 hour to 3 hours at about 15°C to 25°C;
d) filtering the solid separated.

According to another aspect of the present invention, there is provided a novel crystalline form of aripiprazole hydrochloride, designated as Form B, characterized by an x-ray powder diffraction pattern having peaks expressed as 2θ at about 9.3, 14.8, 16.4, 17.4, 18.7, 19.7, 21.4, 21.9, 23.8, 25.1, 25.9, 29.7 degrees. Figure 4 shows typical Form B x-ray powder diffraction pattern.

According to another aspect of the present invention there is provided a process for preparation of the Form B of aripiprazole hydrochloride comprising the steps of:

a) dissolving aripiprazole in a ketonic solvent;
b) adding hydrochloric acid;
c) maintaining for about 1 hour to 4 hours at about 15°C to 25°C;
d) filtering the solid separated.

The ketonic solvent is selected from the group consisting of acetone, methyl isobutyl ketone and methyl ethyl ketone.

According to another aspect of the present invention, there is provided a novel crystalline form of aripiprazole hydrochloride, designated as Form C, characterized by an x-ray powder diffraction pattern having peaks expressed as 2θ at about 3.3, 10.3, 14.2, 14.6, 15.1, 16.4, 16.6, 19.4, 20.3, 20.8, 24.5, 24.9, 25.5, 26.4, 26.7, 28.5, 29.3, 30.1 degrees. Figure 5 shows typical Form C x-ray powder diffraction pattern.
According to another aspect of the present invention there is provided a process for preparation of the Form C of aripiprazole hydrochloride comprising the steps of:

a) dissolving aripiprazole in an ester solvent;

b) adding hydrochloric acid;

c) maintaining for about 1 hour to 4 hours at about 15°C to 25°C;

d) filtering the separated solid.

The ester solvent is selected from the group consisting of ethyl acetate, methyl acetate, ethyl formate and tert-butyl acetate.

According to another aspect of the present invention, there is provided a novel crystalline form of aripiprazole hydrochloride, designated as Form D, characterized by an x-ray powder diffraction pattern having peaks expressed as 2θ at about 9.0, 14.7, 16.4, 17.4, 19.0, 19.3, 19.8, 21.4, 23.4, 24.7, 25.4 degrees. Figure 6 shows typical Form D x-ray powder diffraction pattern.

According to another aspect of the present invention there is provided a process for preparation of the Form D of aripiprazole hydrochloride comprising the steps of:

a) dissolving aripiprazole in tetrahydrofuran;

b) adding hydrochloric acid;

c) maintaining for about 2 hour to 4 hours at about 15°C to 25°C;

d) filtering the solid separated.

According to another aspect of the present invention there is provided a pharmaceutical composition comprising crystalline Form I or Form II of aripiprazole.

According to another aspect of the present invention there is provided a pharmaceutical composition comprising novel crystalline form of aripiprazole hydrochloride.

**BRIEF DESCRIPTION OF THE DRAWINGS**

Figure 1 is a x-ray powder diffraction pattern of crystalline Form I of aripiprazole.

Figure 2 is a x-ray powder diffraction pattern of crystalline Form II of aripiprazole.
Figure 3 is a x-ray powder diffraction pattern of crystalline Form A of aripiprazole hydrochloride.

Figure 4 is a x-ray powder diffraction pattern of crystalline Form B of aripiprazole hydrochloride.

Figure 5 is a x-ray powder diffraction pattern of crystalline Form C of aripiprazole hydrochloride.

Figure 6 is a x-ray powder diffraction pattern of crystalline Form D of aripiprazole hydrochloride.

X-ray powder diffraction spectrum was measured on a Siemens diffractometer.

DETAILED DESCRIPTION OF THE INVENTION

According to one aspect of the present invention, there is provided a novel crystalline form of aripiprazole, designated as Form I, characterized by an x-ray powder diffraction pattern having peaks expressed as 2θ at about 8.7, 11.6, 16.3, 17.7, 18.6, 20.3, 23.4, 24.9 degrees. Figure 1 shows typical Form I x-ray powder diffraction pattern.

According to another aspect of the present invention, there is provided a process for preparation of the Form I of aripiprazole. Thus aripiprazole is dissolved in a suitable solvent. The suitable solvent is selected from the group consisting of acetone, ethyl acetate, methanol and ethanol. Aripiprazole obtained by a known method or crystalline Form II of aripiprazole obtained by the process described below may be used. The solution is refluxed for about 30 minutes to 1 hour. The solution is then cooled slowly to about 15°C to 25°C in about 1 hour and maintained for about 2 hour to 4 hours at the same temperature. The separated crystals are filtered and dried to give Form I of aripiprazole.

According to another aspect of the present invention, there is provided a novel crystalline form of aripiprazole, designated as Form II, characterized by an x-ray powder diffraction pattern having peaks expressed as 2θ at about 12.7, 15.1, 17.5, 18.2, 18.8, 19.5, 20.6, 21.2, 22.6, 23.3, 24.2, 24.9, 27.6, 30.0, 31.6, 35.8 degrees. Figure 2 shows typical Form II x-ray powder diffraction pattern.
According to another aspect of the present invention there is provided a process for preparation of the Form II of aripiprazole, which comprises dissolving aripiprazole in tetrahydrofuran and vacuum drying at about 25°C or spray drying.

According to another aspect of the present invention, there is provided a novel crystalline form of aripiprazole hydrochloride, designated as Form A, characterized by an x-ray powder diffraction pattern having peaks expressed as 2θ at about 6.2, 8.5, 11.5, 15.2, 15.5, 16.8, 17.2, 18.3, 18.9, 19.6, 20.6, 21.3, 23.4, 24.1, 24.7, 25.9, 27.5, 28.3, 28.9, 32.8 degrees. Figure 3 shows typical Form A x-ray powder diffraction pattern.

According to another aspect of the present invention there is provided a process for preparation of the Form A of aripiprazole hydrochloride. Thus aripiprazole is dissolved in ethanol or isopropyl alcohol. If necessary, the solvent may be heated to effect dissolution of aripiprazole. Hydrochloric acid is added to the solution. Hydrochloric acid may be added as an aqueous solution or as a solution in any other solvent; or hydrochloric acid gas may be passed through the solution of aripiprazole. Then the contents are maintained for about 1 hour to 3 hours at about 15°C to 25°C and the separated crystals are filtered and dried to yield Form A of aripiprazole hydrochloride.

According to another aspect of the present invention, there is provided a novel crystalline form of aripiprazole hydrochloride, designated as Form B, characterized by an x-ray powder diffraction pattern having peaks expressed as 2θ at about 9.3, 14.8, 16.4, 17.4, 18.7, 19.7, 21.4, 21.9, 23.8, 25.1, 25.9, 29.7 degrees. Figure 4 shows typical Form B x-ray powder diffraction pattern.

According to another aspect of the present invention there is provided a process for preparation of the Form B of aripiprazole hydrochloride. Thus aripiprazole is dissolved in a ketonic solvent. If necessary, the solvent may be heated to dissolve aripiprazole. The ketonic solvent is acetone or methyl isobutyl ketone or methyl ethyl ketone; or mixture thereof. Hydrochloric acid is added to the solution. Hydrochloric acid may be added as an aqueous solution or as a solution in any other solvent; or hydrochloric acid gas may be passed through the solution of aripiprazole. Then the contents are maintained for about 1 hour to
4 hours at about 15°C to 25°C and the separated crystals are filtered and dried to yield Form B of aripiprazole hydrochloride.

According to another aspect of the present invention, there is provided a novel crystalline form of aripiprazole hydrochloride, designated as Form C, characterized by an X-ray powder diffraction pattern having peaks expressed as 2θ at about 3.3, 10.3, 14.2, 14.6, 15.1, 16.4, 16.6, 19.4, 20.3, 20.8, 24.5, 24.9, 25.5, 26.4, 26.7, 28.5, 29.3, 30.1 degrees. Figure 5 shows typical Form C X-ray powder diffraction pattern.

According to another aspect of the present invention there is provided a process for preparation of the Form C of aripiprazole hydrochloride. Thus aripiprazole is dissolved in an ester solvent. If necessary, the solvent may be heated to effect dissolution of aripiprazole. The ester solvent is selected from the group consisting of ethyl acetate, methyl acetate, ethyl formate and tert-butyl acetate. Hydrochloric acid is added to the solution. Hydrochloric acid may be added as an aqueous solution or as a solution in any other solvent; or hydrochloric acid gas may be passed through the solution of aripiprazole. Then the contents are maintained for about 1 hour to 4 hours at about 15°C to 25°C and the separated solid is filtered and dried to obtain Form C of aripiprazole hydrochloride.

According to another aspect of the present invention, there is provided a novel crystalline form of aripiprazole hydrochloride, designated as Form D, characterized by an X-ray powder diffraction pattern having peaks expressed as 2θ at about 9.0, 14.7, 16.4, 17.4, 19.0, 19.3, 19.8, 21.4, 23.4, 24.7, 25.4 degrees. Figure 6 shows typical Form D X-ray powder diffraction pattern.

According to another aspect of the present invention there is provided a process for preparation of the Form D of aripiprazole hydrochloride. Thus aripiprazole is dissolved in tetrahydrofuran. Hydrochloric acid is added to the solution. Hydrochloric acid may be added as an aqueous solution or as a solution in any other solvent; or hydrochloric acid gas may be passed through the solution of aripiprazole. Then the contents are maintained for 2 hour to 4 hours at about 15°C to 25°C and the separated crystals are filtered and dried to produce Form D of aripiprazole hydrochloride.
The novel crystalline forms of aripiprazole hydrochloride obtained by the processes described above are very pure. So, aripiprazole with high purity can be obtained by basifying a solution of aripiprazole hydrochloride crystalline form and isolating aripiprazole from the solution by usual processes known in the art.

According to another aspect of the present invention there is provided a pharmaceutical composition comprising Form I or Form II of aripiprazole and a pharmaceutically acceptable carrier.

According to another aspect of the present invention there is provided a pharmaceutical composition comprising crystalline form of aripiprazole hydrochloride and a pharmaceutically acceptable carrier. The crystalline form may be Form A, Form B, Form C or Form D.

The forms of aripiprazole or aripiprazole hydrochloride may be formulated in a form suitable for oral administration or injection. The examples of pharmaceutical compositions are tablets, capsules, powders, suspensions, emulsions, injections and the like.

The following examples will serve to further illustrate the invention.

Example 1

Aripiprazole (2 gm) (obtained by a process described in US 5,006,528) is dissolved in acetone (42 ml) and refluxed for 30 minutes. The solution is slowly cooled to 25°C in 1 hour and maintained at 25°C for 3 hours. The separated crystals are filtered and dried to give 1 gm of Form I of aripiprazole.

Example 2

Aripiprazole (2 gm) (obtained by a process described in US 5,006,528) is dissolved in tetrahydrofuran and the solvent is removed by vacuum drying at 25°C for 6 hours to give Form II of aripiprazole in quantitative yield.

Example 3

Aripiprazole (2 gm) (obtained by a process described in US 5,006,528) is dissolved in tetrahydrofuran and the solvent is removed by spray drying at 25°C for 6 hours to give Form II of aripiprazole in quantitative yield.

Example 4
Aripiprazole (2 gm) (obtained by a process described in US 5,006,528) is dissolved in methanol (12 ml) and conc. hydrochloric acid (1 ml) is added to the solution. The contents are maintained for 2 hours at 25°C and the separated solid is filtered to give 2 gm of Form A of aripiprazole hydrochloride.

Example 5

Aripiprazole (2 gm) (obtained by a process described in US 5,006,528) is dissolved in acetone (12 ml) and conc. hydrochloric acid (1 ml) is added to the solution. The contents are maintained for 3 hours at 25°C and the separated solid is filtered to give 1.9 gm of Form B of aripiprazole hydrochloride.

Example 6

Aripiprazole (2 gm) (obtained by a process described in US 5,006,528) is dissolved in ethyl acetate (12 ml). 10% WV HCl in ethyl acetate (4 ml) is added to the solution. The solution is maintained at 25°C for 2 hours and the separated crystals are collected by filtration to give 2 gm of Form C of aripiprazole hydrochloride.

Example 7

Aripiprazole (2 gm) (obtained by a process described in US 5,006,528) is dissolved in tetrahydrofuran (12 ml) and conc. hydrochloric acid (1 ml) is added to the solution. The contents are maintained for 3 hours at 25°C and the separated solid is collected by filtration to give 2 gm of Form D of aripiprazole hydrochloride.

Example 8

Example 1 is repeated using Form II of aripiprazole instead of aripiprazole to give Form I of aripiprazole.

Example 9

Example 2 is repeated using Form I of aripiprazole instead of aripiprazole to give Form II of aripiprazole.

Example 10

Example 5 is repeated using Form I of aripiprazole instead of aripiprazole to give Form B of aripiprazole hydrochloride.
Example 11

Example 7 is repeated using Form II of aripiprazole instead of aripiprazole to give Form D of aripiprazole hydrochloride.
We claim:

1. A crystalline Form I of aripiprazole characterized by an x-ray powder diffraction pattern having peaks expressed as 2θ at about 8.7, 11.6, 16.3, 17.7, 18.6, 20.3, 23.4, 24.9 degrees.

2. A crystalline aripiprazole of claim 1, characterized by an x-ray powder diffraction pattern as in figure 1.

3. A process for preparation of Form I of aripiprazole of claim 1, comprising the steps of:
   a) dissolving aripiprazole in a suitable solvent;
   b) refluxing for about 30 minutes to 1 hour;
   c) cooling slowly to about 15°C to 25°C;
   d) maintaining for about 2 hour to 4 hours at about 15°C to 25°C; and
   e) filtering the solid separated;

   wherein the suitable solvent is selected from the group consisting of acetone, ethyl acetate, methanol and ethanol.

4. A process according to claim 3, wherein the suitable solvent is acetone.

5. A process according to claim 3, wherein the suitable solvent is ethyl acetate.

6. A crystalline Form II of aripiprazole characterized by an x-ray powder diffraction pattern having peaks expressed as 2θ at about 12.7, 15.1, 17.5, 18.2, 18.8, 19.5, 20.6, 21.2, 22.6, 23.3, 24.2, 24.9, 27.6, 30.0, 31.6, 35.8 degrees.

7. A crystalline aripiprazole, characterized by an x-ray powder diffraction pattern as in figure 2.

8. A process for preparation of Form II of aripiprazole of claim 6, which comprises dissolving aripiprazole in tetrahydrofuran and vacuum drying or spray drying at about 25°C.


10. A crystalline aripiprazole hydrochloride, characterized by an x-ray powder diffraction pattern as in figure 3.
11. A process for preparation of Form A of aripiprazole hydrochloride of claim 9, comprising the steps of:
   a) dissolving aripiprazole in methanol or isopropyl alcohol;
   b) adding hydrochloric acid;
   c) maintaining for about 1 hour to 3 hours at about 15\(^\circ\)C to 25\(^\circ\)C;
   d) filtering the solid separated.
12. A process according to claim 11, wherein aripiprazole is dissolved in methanol.
13. A process according to claim 11, wherein aripiprazole is dissolved in isopropyl alcohol.
15. A crystalline aripiprazole hydrochloride, characterized by an x-ray powder diffraction pattern as in figure 4.
16. A process for preparation of Form B of aripiprazole hydrochloride of claim 14, comprising the steps of:
   a) dissolving aripiprazole in a ketonic solvent;
   b) adding hydrochloric acid;
   c) maintaining for about 1 hour to 4 hours at about 15\(^\circ\)C to 25\(^\circ\)C; and
   d) filtering the solid separated;
   wherein the ketonic solvent is selected from the group consisting of acetone, methyl isobutyl ketone and methyl ethyl ketone.
17. A process according to claim 16, wherein the ketone is acetone.
18. A process according to claim 16, wherein the ketone is methyl isobutyl ketone.
20. A crystalline aripiprazole hydrochloride, characterized by an x-ray powder diffraction pattern as in figure 5.
21. A process for preparation of Form C of aripiprazole hydrochloride of claim 19, comprising the steps of:
a) dissolving aripiprazole in an ester solvent;
   b) adding hydrochloric acid;
   c) maintaining for about 1 hour to 4 hours at about 15°C to 25°C; and
   d) filtering the separated solid;

wherein the ester solvent is selected from the group consisting of ethyl acetate, methyl acetate, ethyl formate and tert-butyl acetate.

22. A process according to claim 21, wherein the ester solvent is ethyl acetate.

23. A process according to claim 21, wherein the ester solvent is methyl acetate.


25. A crystalline aripiprazole hydrochloride, characterized by an x-ray powder diffraction pattern as in figure 6.

26. A process for preparation of Form D of aripiprazole hydrochloride of claim 24, comprising the steps of:
   a) dissolving aripiprazole in tetrahydrofuran;
   b) adding hydrochloric acid;
   c) maintaining for about 2 hour to 4 hours at about 15°C to 25°C; and
   d) filtering the solid separated.

27. A pharmaceutical composition comprising the crystalline Form I of aripiprazole of claim 1 and a pharmaceutically acceptable carrier.

28. A pharmaceutical composition comprising the crystalline Form II of aripiprazole of claim 6 and a pharmaceutically acceptable carrier.

29. A pharmaceutical composition comprising a crystalline form of aripiprazole hydrochloride and a pharmaceutically acceptable carrier.

30. A pharmaceutical composition as defined in claim 29, wherein the crystalline form is Form A, Form B, Form C or Form D.
fig. 2
fig. 3

[Graph with labeled axes: Lin (Counts) and 2-Theta - Scale]
### INTERNATIONAL SEARCH REPORT

**CLASSIFICATION OF SUBJECT MATTER**

**IPC**: C07D 215/227; A61K 31/47

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)

**IPC**: C07D, 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)

**EPOQUE**

#### C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<th>Category</th>
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<td>EP 0367141 A2 (OTSUKA PHARMACEUTICAL CO) 9 May 1990 (09.05.90) page 9, example 1; page 13, examples 5,10.</td>
<td>1,3-6,8,9,11-14,16-19,21-24,27-30</td>
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☐ Further documents are listed in the continuation of Box C.  ☑ See patent family annex.

* Special categories of cited documents:
  * "A" document defining the general state of the art which is not considered to be of particular relevance
  * "E" earlier application or patent but published on or after the international filing date
  * "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  * "O" document referring to an oral disclosure, use, exhibition or other means
  * "P" document published prior to the international filing date but later than the priority date claimed
  * "R" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
  * "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
  * "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
  * "&" document number of the same patent family

**Date of the actual completion of the international search**

5 November 2003 (05.11.2003)

**Date of mailing of the international search report**


Name and mailing address of the ISA/AT

Austrian Patent Office

Dresdner Straße 87, A-1200 Vienna

Facsimile No. 1/53424/535

Authorized officer

KOLLER G.

Telephone No. 1/53424/458

Form PCT/ISA/210 (second sheet) (July 1998)
**INTERNATIONAL SEARCH REPORT**

**Box I** Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

1. □ Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 2, 7, 10, 15, 20, 25 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:

   Claims 2, 7, 10, 15, 20 and 25 refer to figures of the drawing and contravene Rule 6.2(a) PCT.

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

**Box II** Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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.

2. □ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

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

4. □ 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 claims Nos.:  

**Remark on Protest**

□ The additional search fees were accompanied by the applicant's protest.

□ No protest accompanied the payment of additional search fees.
### INTERNATIONAL SEARCH REPORT
Information on patent family members

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PCT/ISA/210 (patent family annex) (July 1998)