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(54) Title: PHARMACEUTICAL FORMULATIONS COMPRISING A SALT OF CLAVULANIC ACID, VANCOMYCIN AND ONE OR MORE BETA-LACTAM ANTIBIOTICS

(57) Abstract

Pharmaceutical formulations comprising a pharmaceutically acceptable salt of clavulanic acid, particularly potassium clavulanate, in combination with vancomycin, and one or more β-lactam antibiotics particularly sodium amoxycillin or sodium ticarcillin. The formulations are suitable for parenteral administration in the treatment of methicillin resistant staphylococcal infection.

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Pharmaceutical formulations comprising a salt of clavulanic acid, vancomycin and one or more beta-lactam antibiotics

This invention relates to pharmaceutical formulations, in particular to novel uses of formulations in connection with the treatment of infection by bacteria.

The increasing incidence of infections due to methicillin resistant staphylococci ("MRS") has become a serious clinical problem worldwide. Most of these organisms are resistant to a number of drugs, posing a serious challenge to antimicrobial therapy. Glycopeptides are the main treatment for MRS infections and bacterial resistance to this class of compounds would have major implications.

Vancomycin is a known glycopeptide antibiotic, usually administered in the form of its hydrochloride. The term "vancomycin" used herein includes vancomycin itself and all its pharmaceutically acceptable derivatives.

The invention provides a pharmaceutical formulation which comprises a pharmaceutically acceptable salt of clavulanic acid, in combination with vancomycin one or more β-lactam antibiotics.

The present invention also provides a method of use of a pharmaceutically acceptable salt of clavulanic acid and vancomycin, and one or more β-lactam antibiotics, together in combination in the manufacture of a medicament formulation, particularly a formulation for the treatment of infection of humans or animals by bacteria.

The present invention further provides a method for the preparation of a pharmaceutical formulation as defined above, which method comprises admixing the combination of a pharmaceutically acceptable salt of clavulanic acid, and vancomycin and one or more β-lactam antibiotics.

As salts of clavulanic acid are extremely hygroscopic such formulations must be prepared in dry conditions, typically at a relative humidity of 30% or less. All constituents of the formulation should be predried. Dry formulations for aqueous reconstitution may be made up with an aqueous vehicle shortly before use.

The present invention further provides a pharmaceutical formulation as defined above for use as an active therapeutic substance, particularly in the treatment of infection of humans or animals by bacterial infections.

The present invention also provides the use of a pharmaceutically acceptable salt of clavulanic acid to enhance the antibacterial effectiveness of the combination of vancomycin and one or more β-lactam antibiotics.

Further the invention provides a method for the treatment of an infection by bacteria in humans or animals, which comprises administering thereto, simultaneously or successively in any order, a pharmaceutically acceptable salt of clavulanic acid and vancomycin, and one or more β-lactam antibiotics. Typically

the clavulanic acid and vancomycin may be co-administered together, optionally also together with one or more β-lactam antibiotics, e.g. as a pharmaceutical composition.

The formulations and methods of the invention are suitable for use in the treatment of infection by bacteria in humans or animals, particularly of MRS, for example *Staphylococcus aureus* and *Staphylococcus epidermis*.

The most pharmaceutically stable salt of clavulanic acid is the potassium salt, i.e. potassium clavulanate.

Suitable β-lactam antibiotics which may be included in the formulations and methods of this invention as described herein include penicillins and cephalosporins. Suitable antibiotics include those for example listed in GB 1578739, e.g. on page 3 line 25 to 36 thereof.

Suitable β-lactam antibiotics include the penicillins: amoxycillin, ampicillin, apalcillin, aspoxicillin, azidocillin, azlocillin, aztreonam, benzyl-penicillin, bacampicillin, carbenicillin, cloxacillin, cyclacillin, dicloxicillin, epicillin, flucloxacillin, lenampicillin, mecillinam, methicillin, mezlocillin, phenoxymethylpenicillin, piperacillin, pivampicillin, propicillin, sulbenicillin, talampicillin, and ticarcillin; and the cephalosporins: cefaclor, cefadroxil, cefatrizine, cefclidine, cefamandole, cefazolin, cefbuperazone, cefcanel daloxate, cefdinir, cefepime, cefetamet pivoxil, cefixime, cefminox, cefminoxime,. cefmetazole, cefonicid, cefoperazone, cefotaxime, cefotetan, cefotiam, cefotiam hexetil, cefoxitin, cefpimizole, cefpiramide, cefrirome, cefpodoxime proxetil ,cefprozil, ceftazidime, ceftibuten, ceftizoxime, ceftriaxone, cefuroxime axetil, cefuroxime, cephacetrile, cephalexin, cephaloridine, cephalothin, cephamanadole nafate, cephapirin, cephoperazone, cefsulodin, cefuzonam, cephradine, loracarbef, DQ 2556, ME1207, S-1006, SCE-2787 and moxalactam.

Amoxycillin and ticarcillin are preferred β-lactam antibiotics, for example amoxycillin used in the form of sodium amoxycillin, for example as spray-dried sodium amoxycillin or as anhydrous crystalline sodium amoxycillin in the form described in EP 0131147, and ticarcillin in the form of its sodium salt.

The clavulanic acid and vancomycin and β-lactam antibiotics, as used in this invention, whether in the form of the free acids, salts, esters or derivatives thereof are preferably each in a substantially pure form, e.g. at least 60% pure, more suitably at least 75% pure, preferably at least 85% especially at least 98% pure on a weight basis.

The formulations of the invention may be in a form adapted for parenteral use, i.e. the manner in which vancomycin is normally administered and may be

used for the treatment of infection in humans and animals especially mammals, including in particular domesticated animals (including farm animals).

The formulations of the invention may, for example, be made up in the form of tablets, suspensions, solutions, reconstitutable powders, and sterile forms suitable for injection or infusion. Such formulations may contain conventional pharmaceutically acceptable materials, for example solid or liquid diluents, colours and preservatives, in accordance with conventional pharmaceutical practice in a manner well understood by those skilled in the art of formulating antibiotics. Normally all such ingredients are predried. Aqueous solutions are normally provided in the form of dry ingredients for reconstitution immediately prior to use.

It can be particularly advantageous for the formulations of the invention to be administered to a patient by injection or infusion. That method of administration has the advantage of rapidly resulting in high blood levels of the active ingredient compounds being administered. Accordingly, in one preferred form of the formulation of the invention, the compounds are present in sterile form, including in sterile crystalline form. A further preferred form of the formulation of the invention, is one in which the formulation is in injectable or infusable form.

One injectable or infusable form of the formulation of the invention is an injectable or infusable solution, which suitably comprises an aqueous solution of a pharmaceutically acceptable salt of clavulanic acid and vancomycin, and optionally one or more other antimicrobial agents, in a sterile pyrogen-free liquid, for example water or aqueous ethanol. Because of the water sensitivity of salts of clavulanic acid such a formulation should be provided as the dry constituents and be made up with water immediately prior to use.

A further injectable or infusable form of the formulation of the invention is an injectable or infusable suspension, in which case the salt of clavulanic acid, and vancomycin are advantageously present in finely particulate form. The suspension may be an aqueous suspension in, for example, sterile water or sterile saline, which may additionally include a suspending agent, for example polyvinylpyrrolidone. Alternatively, the suspension may be an oily suspension in a pharmaceutically acceptable oil suspending agent, for example arachis oil, which should be dry. Because of the water sensitivity of clavulanic acid salts such aqueous suspensions should be made up from dry constituents immediately prior to use.

A formulation according to the invention may be in unit dosage form, for example unit dosage form for parenteral administration, which will primarily include administration by injection or infusion, especially intramuscular and intravenous administration. The formulation may comprise the vancomycin, and the β-lactam antibiotic / clavulanate combination presented in separate dosage forms,

for administration together or sequentially. For example these constituents and suitable excipients (which will be apparent to those skilled in the art) may be presented in separate vials for making up into a solution or suspension for injection or infusion.

In the formulations and methods according to the invention, the vancomycin may be administered to the patient in an antibacterially effective amount, and the salt of clavulanic acid may be administered in an amount effective to inhibit β-lactamase enzymes.

The salt of clavulanic acid, particularly potassium clavulanate, will generally be administered in an amount sufficient to inhibit the β-lactamase enzyme(s) associated with infecting bacterial and/or bacterial organism(s). To that end, it may suitably be administered to the patient at a daily dosage of from 0.3 to 15 mg/kg, preferably from 0.7 to 10 mg/kg, for example from 0.7 to 7 mg/kg, of body weight, expressed in terms of parent clavulanic acid. For an adult human (of approximately 70 kg body weight), from 25 to 1000 mg, preferably from 50 to 500 mg, of the salt of clavulanic acid may be administered daily, suitably in from 1 to 6, preferably from 2 to 4, separate doses. Higher or lower dosages may, however, be used in accordance with clinical practice.

When the formulations according to the invention are presented in unit dosage form, each unit dose may suitably comprise from 12.5 to 1000 mg, preferably from 12.5 to 250 mg, of the salt of clavulanic acid. Each unit dose may, for example, be 12.5, 25, 50, 75, 100, 125, 150, 200, or 250 mg of the salt of clavulanic acid.

The ratio of the amount of the salt of clavulanic acid used according to the invention : amount of β-lactam antibiotic(s) present may vary within a wide range, e.g. 1:1 to 1:30 by weight. In the case of amoxycillin the said ratio may, for example, be from 1:1 to 1:12; more particularly, it may, for example, be from 1:1 to 1:7, 1:1 to 1:4 or 1:1 to 1:2, by weight.

The amount of any β-lactam antibiotic(s), such as amoxycillin or ticarcillin, e.g. as the respective sodium salt in a formulation according to the invention will normally be approximately similar to the amount in which it is conventionally used *per se*. In the case of amoxycillin for example from 125 to 3000 mg per day, and from 125 to 3000 mg per unit dose, advantageously from about 125 to 1000 mg per unit dose, from 2 to 4 times daily may be administered. In the case of ticarcillin for example a maximum of 5 g eight hourly, or 7g twelve hourly may be administered. These weights are expressed in terms of the parent free acids.

The amount of vancomycin, e.g. as the hydrochloride, in a formulation according to the invention will normally be approximately similar to the amount in

which it is conventionally used *per se*. For example in the case of adults up to 2000 mg per day may be administered, typically in divided doses by i.v. infusion over 60 minutes, and in the case of children up to 40 mg/kg daily in divided doses by slow i.v. infusion over 60 minutes. These weights are expressed in terms of the parent free acid.

An example of a suitable formulation for parenteral administration according to this invention is one comprising from 12.5 to 250mg, preferably from 25 to 125 mg, of potassium clavulanate, in admixture or conjunction with 100 to 500 mg of vancomycin thereof per unit dose, optionally also comprising 125 to 3000 mg of sodium amoxycillin or sodium ticarcillin.

The following examples illustrate the invention. In these examples the abbreviation AMX is used for amoxycillin and CA is used for clavulanic acid, used in the form of potassium clavulanate.

Example 1: Enhanced efficacy of amoxycillin / clavulanate in combination with vancomycin against experimental staphylococcal endocarditis in rats.

Animals were infected with i.v. *S. aureus* E164 (MRSA) to produce endocarditis. Therapy (s.c.) was initiated at either 8 or 24 h post infection and continued for 4 days. Vegetations were harvested 96h post infection or at death if occurring earlier. Amoxycillin / clavulanate (200/20 mg/kg) + vancomycin (80 mg/kg) administered at 8h post infection reduced bacterial numbers significantly (3.4 ± 2.4 $\log_{10}$cfu/veg; $p < 0.01$) compared with either agent given alone (5.9 ± 2.5 and 6.3 ± 2.5 $\log_{10}$cfu/veg respectively). Reducing either the amoxycillin / clavulanate (100/20 mg/kg) or the vancomycin (40 mg/kg) component did not result in loss of efficacy with the antibiotic combination. Where therapy was delayed until 24h post infection, bacterial numbers for amoxycillin clavulanate (100/20 mg/kg) or vancomycin (80 mg/kg) were not significantly different ($p > 0.05$) to untreated controls. In contrast, combination therapy (amoxycillin / clavulanate 100/20 mg/kg + vancomycin 80mg/kg) resulted in a marked 2.5-3 log reduction ($p < 0.05$) in viable bacterial numbers.

Example 2: Synergistic activity of vancomycin and ticarcillin / clavulanate against MRS.

FICs were determined in chequerboard tests for ticarcillin / clavulanate and vancomycin against 19 MRS. Synergy was demonstrated against 6/14 MRSA and 5/5 methicillin resistant *stapylococcus epidermis* (MRSE). Additivity was observed with all other strains. Bactericidal activity of these agents alone and in combination was assessed by viable count and flow cytometry (FC). Vancomycin at 0.25 mcg/ml

(1/4 MIC) had no effect and ticarcillin / clavulanate at 8/2 mcg/ml was essentially bacteriostatic. However vancomycin at 0.25 mcg/ml in combination with ticarcillin / clavulanate at 2/2 mcg/L was rapidly bactericidal, the viable count being reduced by 3 log10 after 8 hours with little regrowth over a 24 hour exposure. FC analysis supported the viable count results. These data indicate the combination of ticarcillin / clavulanate and vancomycin to be highly effective in the eradication of MRS in vitro.

Example 3: Synergistic activity of vancomycin and amoxycillin / clavulanate against MRSE.

Methicillin resistant *stapylococcus epidermis* 100710 was cultured overnight in 9ml Difco Mueller (MH) broth at 37°C. At time zero 20 ml of pre-warmed MH broth was inoculated with 20 mc.L of the starter culture (10^{-3} diln.) in 100 ml conical flasks. Antibiotic concentrations were added to measured concentrations and the following results were observed:

AMX/CA at MIC (1/0.5 mcg/ml) was essentially bacteriostatic over the first 8 hours with a 2 $\log_{10}$ increase in growth by 24 hours.

Vancomycin at MIC (4.00 mcg/ml) was rapidly bactericidal. A 4 $\log_{10}$ drop in cell viability was observed over 6 hours with no subsequent regrowth at 24 hours.

Both AMX/CA and vancomycin at 1/4 MIC had no effect on cell viability, treated cells followed a similar growth pattern as the untreated control.

AMX/CA at MIC (1/0.5 mcg/ml) plus vancomycin at 1/4 MIC (1.00 mcg/ml) was rapidly bactericidal. A 4 $\log_{10}$ drop in cell viability was noted over the first 4 hours with no subsequent regrowth of MRSE 100710 at 24 hours.

In combination AMX/CA at 0.25 mcg/ml and vancomycin at 1.00 mcg/ml were rapidly bactericidal a 2.5 $\log_{10}$ drop in viability being observed over 8 hours with no regrowth by 24 hours.

These results indicate that in combination AMX/CA and vancomycin at sub-MIC levels act to produce a synergistic effect in the eradication of MRSE 100710 *in vitro*.

Example 4: Efficacy of amoxycillin / clavulanate co-administered with vancomycin against experimental endocarditis in rats caused by methicillin resistant *staphylococcus aureus*.

Male CD rats (Charles River) weighing approximately 120-150g were experimentally induced with endocarditis by a known protocol (Heraief et al. (1982) *Natural history of aortic valve endocarditis in rats*. Infect. Immun. 37; 127-31).

The rats were infected intravenously via the caudal vein with approximately 6 log 10 cfu of S. *aureus*. The strains chosen had AMX/CA susceptibilities of 8/4 mcg/ml and 16/8 mcg/ml. S. *aureus* P8+ (AMX/CA MIC 8/4 mcg/ml) is a heterogeneously resistant clinical isolate which is a potent producer of penicillinase. S. *aureus* E164 and 468 are typical AMX/CA resistant clinical isolates of MRSA having MIC values of 16/8 mcg/ml.

AMX/CA and vancomycin were administered to infected rats by subcutaneous injection to groups of rats commencing 8h, 12h or 24h post infection and continuing t.i.d or q.i.d for 3 or 4 days. Further groups of rats received phosphate buffered saline and served as controls. Animals were weighed daily and were assessed for signs of endocarditis at least 5 times daily.

Results showed that for *S. aureus* P8+ a good response was seen with vancomycin monotherapy, which was not enhanced by co-administration of AMX/CA. But the survival rate for animals dosed with vancomycin was slightly lower (88%) compared with those dosed with vancomycin + AMX/CA (100%). For *S. aureus* E164 which has an AMX/CA MIC of 16/8 mcg/ml, when AMX/CA 200/20 mg/kg was given in combination with vancomycin 40 or 80 mg/kg a significant reduction ($p=0.01$) in bacterial numbers was obtained, compared with AMX/CA or vancomycin alone. With *S. aureus* 468 an enhanced activity was also seen when using the combination AMX/CA and vancomycin.

The results showed that enhancement of activity, determined by lower mean bacterial numbers in aortic vegetations, increased sterilisation of vegetations and improved survival rate was achieved with AMX/CA when co-administered with vancomycin compared with either agent given alone against these strains of *S. aureus*.

Example 5: Synergistic activity of vancomycin and ticarcillin /clavulanate against methicillin resistant staphylococcus aureus V12181.

20 ml of MH broth containing AMX/CA and vancomycin, singly or in combination was inoculated with approximately 10^5 cfu/ml from an overnight broth of MRSA V12181. The cultures were incubated at 37°C in a shaking incubator and samples taken at appropriate time points for viable cell number determination.

The following MRSA and MRSE strains were also investigated in this manner: MRSA strains; V573, V1 1268, 468, ROWBOTTOM, 68/8684, V331, W0206, 453, E164, V8535, V924, 13136mec2a+bla+, 13136mec2a+bla-, MRSE strains; 3/02302, S1187, 100710, 57811, 59356.

Synergy, defined as an FIC of ≤ 0.5 was noted with 6/14 MRSA and 5/5 MRSE, was observed in vitro between ticarcillin/clavulanate in this experiment.

Against MRSA concentrations of ticarcillin / clavulanate and vancomycin that were not bactericidal in their own right, were rapidly bactericidal in combination, even at 1/4 MIC, and there was no regrowth by 24 hours.

Example 6: Effect of extended dosing schedules of amoxycillin/ clavulanate co-administered with vancomycin against experimental endocarditis in rats caused by methicillin-resistant Staphylococcus aureus.

The effect of an extended dosing schedule (6 days) of amoxycillin/ clavulanate in combination with vancomycin was determined using an experimental model of bacterial endocarditis in rats. Following surgery, animals were infected intravenously using *S. aureus* 468. Subcutaneous therapy was initiated at 12h post infection and the doses administered were chosen to approximate in the rat, the peak serum concentrations measured in man following parenteral therapy for serious infections.

Treatment continued t.i.d for 3 or 6 days and aortic valve vegetations were harvested for bacterial enumeration at 96h or 168h post infection or at death if occurring earlier. Extending the dosing period from 3 to 6 days resulted in significantly($p < 0.01$) improved efficacy as demonstrated by lower mean bacterial numbers in aortic vegetations, a higher percentage of vegetations sterilised and increased survival rate. These data emphasise the importance of the length of the dosing period in obtaining better therapeutic outcomes with amoxycillin/clavulanate co-administered with vancomycin.

Claims:

1. A pharmaceutical formulation which comprises a pharmaceutically acceptable salt of clavulanic acid, in combination with vancomycin, and one or more β-lactam antibiotics.

2. A method of use of a pharmaceutically acceptable salt of clavulanic acid and vancomycin, and optionally one or more β-lactam antibiotic, together in combination in the manufacture of a medicament formulation for the treatment of infection of humans or animals by bacteria.

3. A method for the preparation of a pharmaceutical formulation as claimed in claim 1, which method comprises admixing the combination of a pharmaceutically acceptable salt of clavulanic acid, and vancomycin and one or more β-lactam antibiotics.

4. A pharmaceutical formulation as claimed in claim 1 for use as an active therapeutic substance in the treatment of infection of humans or animals by bacterial infections.

5. The use of a pharmaceutically acceptable salt of clavulanic acid to enhance the antibacterial effectiveness of a combination of vancomycin and one or more β-lactam antibiotics.

6. A method for the treatment of an infection by bacteria in humans or animals, which comprises administering thereto, simultaneously or successively in any order, a pharmaceutically acceptable salt of clavulanic acid and vancomycin, and optionally one or more β-lactam antibiotics.

7. A formulation according to any one of preceding claims 1, 2 or 4, characterised in that the clavulanate is present as potassium clavulanate, and the β-lactam antibiotic amoxycillin or ticarcillin is present in the formulation or used in the method.

8. A method according to any one of preceding claims 3, 5 or 6, characterised in that the clavulanate is present as potassium clavulanate, and the β-lactam antibiotic amoxycillin or ticarcillin is present in the formulation or used in the method.

9. A formulation according to claim 1 or 7 characterised in that the vancomycin, and the β-lactam antibiotic / clavulanate combination are presented in separate dosage forms for administration together or sequentially.

10. A formulation according to claim 1 characterised by being a formulation for parenteral administration comprising from 12.5 to 250mg of potassium clavulanate, in admixture or conjunction with 100 to 500 mg of vancomycin thereof per unit dose and also comprising 125 to 3000 mg of sodium amoxycillin or sodium ticarcillin.

INTERNATIONAL SEARCH REPORT

Ir ıtional Application No
PCT/EP 96/00302

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/14 //(A61K38/14,31:43,31:42)

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 6 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 practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PEDIATRIC HEMATOLOGY AND ONCOLOGY, 11 (2). 1994. 181-187., XP000057868 YU L C ET AL: "The efficacy of ticarcillin-clavulanate and gentamicin as empiric treatment for febrile neutropenic pediatric patients with cancer" see page 186, paragraph 3 ---	1-10
X	CANCER, JAN 1 1990, 65 (1) P9-16, UNITED STATES, XP000572867 BODEY GP ET AL: "Beta-lactam regimens for the febrile neutropenic patient." see abstract ---	1-10
	-/--	

[X] Further documents are listed in the continuation of box C. [ ] Patent family members are listed in annex.

* Special categories of cited documents :

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"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

"T" 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 member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
12 June 1996	27.06.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Leherte, C

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AM. J. MED., 1985, 79/5B (62-66), USA, XP002005423 FAINSTEIN V. ET AL: "Ticarcillin plus clavulanic acid in the treatment of patients with cancer" see abstract -----	1-10

1

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/EP 96/00302

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. [X] Claims Nos.: 6
because they relate to subject matter not required to be searched by this Authority, namely:
REMARK: Although claim 6 is directed to a method of treatment of (diagnosti c method practised on) the human/animal body the search has been carried ou t and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
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. [ ] 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 searches 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.