AUSTRALIA

PATENTS ACT 1990

NOTICE OF ENTITLEMENT

We, **KABI PHARMACIA AB**, the applicant/Nominated Person in respect of Application No. 14280/92 state the following:-

The Nominated Person is entitled to the grant of the patent because the Nominated Person derives title to the invention by assignment from the inventors.

The Nominated Person is entitled to claim priority from the application listed in the declaration under Article 8 of the PCT because the Nominated Person is the applicant in respect of the application listed in the declaration under Article 8 of the PCT, and because that application was the first application made in a Convention country in respect of the invention.

DATED this 28th day of April, 1993

.....

a member of the firm of DAVIES COLLISON CAVE
for and on behalf of the applicant(s)

AU9214280

(12) PATENT ABRIDGMENT (11) Document No. AU-B-14280/92
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 653797

(54) Title
NEW USE OF DIPHENYLBUTYL-PIPERAZINECARBOXAMIDES IN THE TREATMENT OF SUBSTANCE DISORDERS

(51)[5] International Patent Classification(s)
A61K 031/495

(21) Application No. : 14280/92 (22) Application Date : 23.03.92

(87) PCT Publication Number : WO92/16211

(30) Priority Data

(31) Number	(32) Date	(33) Country
9100860	22.03.91	SE SWEDEN

(43) Publication Date : 21.10.92

(44) Publication Date of Accepted Application : 13.10.94

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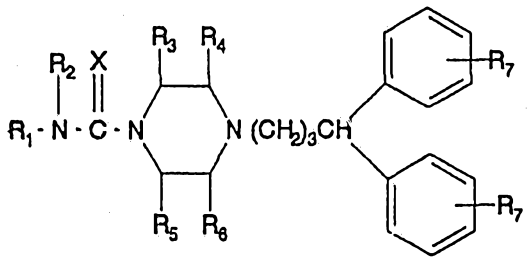
(57) Claim

1. A method for the relief or prevention of a withdrawal syndrome resulting from addiction to a drug or substance of abuse and/or for the suppression of dependence on drugs or substances of abuse which comprises administering an effective amount of a diphenylbutyl-piperazinecarboxamide of the formula



wherein

R_1 and R_2 are groups independently selected from the group of H, alkyl chains, straight or branched, with 1-10 carbon atoms, cycloalkyl with 3-8 carbon atoms, aralkyl with 7-9 carbon atoms, alkenyl with 2-10 carbon atoms, phenyl unsubstituted or substituted by one to three groups selected from halogen, especially F, Cl and Br, lower alkyl with 1-5 carbon atoms, lower alkoxy with 1-5 carbon atoms, amine unsubstituted or

.../2

substituted by one or two lower alkyl groups with 1-5 carbon atoms, $-CF_3$ and -CN groups,

R_3, R_4, R_5 and R_6 are groups independently selected from H, lower alkyl having from 1-3 carbon atoms and phenyl,

R_7 is selected from hydrogen, halogen especially F, Cl and Br, lower alkoxy with 1-3 carbon atoms and $-CF_3$, and

X is O or S,

or a physiologically acceptable salt thereof,

to a person in need of such treatment.

3. A method according to claim 1 or claim 2, wherein the diphenylbutyl-piperazinecarboxamide is amperozide, 4-[4,4-bis(4-fluorophenyl)butyl]-N-ethyl-1-piperazinecarboxamide or a physiologically acceptable salt thereof.

OPI DATE 21/10/92 APPLN. ID 14280 / 92
AOJP DATE 26/11/92 PCT NUMBER PCT/SE92/00182
INTEI ION TREATY (PCT)

(51) International Patent Classification 5 :
A61K 31/495, C07D 295/215

A1

(11) International Publication Number: WO 92/16211
(43) International Publication Date: 1 October 1992 (01.10.92)

(21) International Application Number: PCT/SE92/00182
(22) International Filing Date: 23 Mar 1992 (23.03.92)

(30) Priority data:
9100860-7 22 March 1991 (22.03.91) SE

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(72) Inventors; and
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(81) Designated States: AT (European patent), AU, BB, BE (European patent), BG, BR, CA, CH (European patent), CS, DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU (European patent), MC (European patent), MG, MN, MW, NL (European patent), NO, PL, RO, RU, SD, SE (European patent), US.

Published
With international search report.

653797

(54) Title: NEW USE OF DIPHENYLBUTYL-PIPERAZINECARBOXAMIDES IN THE TREATMENT OF SUBSTANCE DISORDERS

(57) Abstract

New use of certain diphenylbutyl-piperazinecarboxamides, especially amperozide, 4-[4,4-bis(4-fluorophenyl)butyl]-N-ethyl-1-piperazinecarboxamide, and salts thereof, in the treatment of substance abuse disorders. More particularly, this treatment relates to the amelioration of withdrawal symptoms and to modifying drug-seeking behaviour.

NEW USE OF DIPHENYLBUTYL-PIPERAZINECARBOXAMIDES IN THE TREATMENT OF SUBSTANCE DISORDERS

FIELD OF THE INVENTION

The present invention relates to a new use of certain diphenylbutyl-piperazinecarboxamides, especially amperozide, 4-[4,4-bis(4-fluorophenyl)butyl]-N-ethyl-1-piperazinecarboxamide, and salts thereof, in the treatment of substance abuse disorders. More particularly, this invention relates to the amelioration of withdrawal symptoms and to modifying drug-seeking behaviour.

BACKGROUND OF THE INVENTION.

Different classes of neuronal receptors and neurotransmitters in the brain have been implicated in the complex mechanisms underlying the compulsive drinking of alcohol. Experimental findings have favoured the opioid, dopaminergic, serotonergic, and benzodiazepine receptor subtypes. Whether the receptor category is pre- or postsynaptic in nature and whether neurotransmitter synthesis and/or release is equally involved in the manifestation of alcohol drinking is presently unknown.

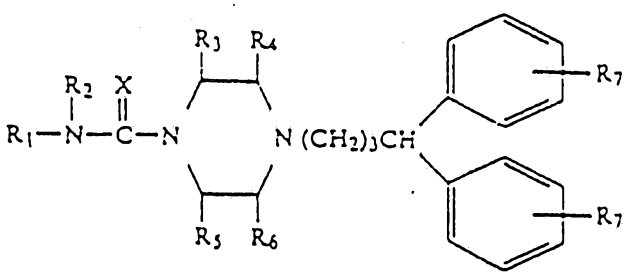
Drug dependency is extremely difficult to escape. This is true whether the dependency is one based on ethanol, amphetamine, barbiturates, benzodiazepines, cocaine, nicotine, opioids, and phencyclidine or the like. Despite active research, there are as yet no drugs that specifically can antagonize for example the alcohol craving in alcohol-dependent subjects. Previous research demonstrated that for example serotonin uptake blockers (e.g. zimelidine, sertraline) reduce voluntary alcohol consumption in rats and humans. However, the mechanism of action of these compounds is not well understood. There is considerable experimental evidence that the effects on alcohol intake may be an expression of a more general inhibiting role that serotonin plays in consummatory behaviour. Indeed

serotonin uptake blockers and serotonin agonists have been shown to reduce a number of oral consummatory behaviours such as the intake of food as well as a variety of flavoured fluids such as alcohol.

The serotonin uptake blocker, sertraline, has been found to reduce alcohol intake in rats. Concurrent with the effect on alcohol drinking, however, sertraline lowered the intake of food and water and caused an overall decline in body weights (Gill K. et al., Alcohol 5:355-358, 1988; Myers R.D. and Quarfordt S.D., Pharmacol. Biochem. Behav. 40:923-28, 1991). Clearly, it is likely that the action of sertraline on alcohol intake is related to a serotonin uptake blocker's effect on oral consummatory behaviour. Hence, a decline also in the drinking of alcohol would not be unexpected. Furthermore, during the period following the sertraline treatment, the intake of alcohol rose toward the pretreatment level. There is accordingly a need for a more specific and effective agent to be used for treating abuse disorders.

SUMMARY OF THE INVENTION.

It has now unexpectedly been found that diphenylbutyl-piperazinecarboxamides of the formula



(I)

wherein

R_1 and R_2 are groups independently selected from the group of H, alkyl chains, straight or branched, with 1-10 carbon atoms, cycloalkyl with 3-8 carbon atoms, aralkyl with 7-9 carbon atoms, alkenyl with 2-10 carbon atoms, phenyl unsubstituted or substituted by one to three groups selected from halogen, especially F, Cl and Br, lower alkyl with 1-5 carbon atoms, lower alkoxy with with 1-5 carbon atoms, amine unsubstituted

or substituted by one or two lower alkyl groups with 1-5 carbon atoms, $-CF_3$ and -CN groups,
R_3, R_4, R_5 and R_6 are groups independently selected from H, lower alkyl having from 1-3 carbon atoms and phenyl,
R_7 is selected from hydrogen, halogen especially F, Cl and Br, lower alkoxy with 1-3 carbon atoms and $-CF_3$, and
X is O or S
and pharmaceutically acceptable salts thereof,

are extremely effective and specific in suppression of alcohol dependence.

This finding opens up a completely new method of treating dependence on drugs, alcohol, nicotine and the like. The actual substances have been found to be both chemically and pharmacologically different from those drugs suggested hitherto for the treatment of drug dependence.

Specifically the invention relates to the relief or prevention of a withdrawal syndrome resulting from addiction to a drug or substance of abuse and/or for the suppression of dependence on drugs or substances of abuse.

The substances as such are known from the prior art (see US Patent 4308387, which is hereby incorporated by reference) as well as their use use in other areas of medicine (see US Patents 4447433, 4385057 and 5013735).

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a method for treating substance abuse disorders by administering to a patient suffering from abuse a therapeutically effective amount of a diphenylbutyl-piperazinecarboxamide according to Formula I, as defined above. The at present preferred substances are those wherein
R_1 is methyl, ethyl or n-, iso- or cyclopropyl,
R_2 is H,

R_3, R_4, R_5 and R_6 are hydrogen or R_3 and R_6 are hydrogen and R_4 and R_5 are methyl, or R_4 and R_5 are hydrogen and R_3 and R_6 are methyl,
R_7 is hydrogen or halogen, preferrably one substituent on each benzene ring being F, and
X is O,

or physiologically acceptable salts thereof.

The most preferred substance at present is amperozide or a physiologically acceptable salt thereof. Amperozide, with the chemical name 4-[4,4-bis(4-fluorophenyl)butyl]-N-ethyl-1-piperazinecarboxamide, is a psychotropic compound developed by Björk A.K.K. et al (U.S. Patent No. 4308387) with effects preferentially on emotional behaviour mediated by an action on the limbic brain areas (Christensson E. and Björk A., Pharmacol. Toxicol. 66: Suppl. I, 5-7, 1990). While the mechanism by which amperozide affects emotional behaviour remains unknown, research indicates that amperozide is a serotonergic antagonist (Svartengren J. and Simonsson P.,Pharmacol. Toxicol. 66: Suppl. I, 8-11, 1990) and, furthermore, acts as a serotonin uptake blocker (Eriksson E., Life Sci. 47:2111-2117, 1990). Recent findings suggest that amperozide modifies also the glutaminergic neurotransmission that would be of importance for learning and memory.

In said article by Eriksson E., a statement is cited telling that "serotonin uptake inhibitors might be useful in the treatment of abuse, e.g. citalopram and zimelidine, which appear to suppress the abuse fo alcohol". However, there is in said article no mention of the fact that serotonin uptake blockers have been shown to reduce a number of oral consummatory behaviours. Apparently, a serotonin uptake blockade does not in itself constitute the basis for a pharmacological specificity of action in the treatment of substance abuse disorders. Hence, the general statement in said article by Eriksson E. does not give a man of ordinary skill in the art the basis for selecting substances which meet

the need for more specific and effective agents to be used in the treatment of substance abuse disorders.

The invention is also related to the use of a therapeutically effective amount of a substance according to Formula 1 for preparation of a composition for the treatment of substance abuse disorders, as well as to the composition as such.

Repeated administration to a subject of certain drugs such as opiates, (e.g. morphine), cocaine, benzodiazepines (e.g. diazepam), or substances of abuse such as alcohol or nicotine can lead to physical and/or psychological dependence upon that drug or substance. When the drug or substance of abuse is withdrawn from a dependent subject, the subject develops certain symptoms including sleep and mood disturbance and intense craving for the drug or substance of abuse. These symptoms may be collectively described as a withdrawal or abstinence syndrome in connection with the present invention.

Formulations comprising the pharmacologically active compounds of this invention are disclosed in U.S. Patents No. 4308387, 4385057, and 5013735 which are hereby incorporated by reference. As examples of such formulations, expected to be suitable for use for treatment of substance abuse disorders, can be mentioned:

Capsules containing (per capsule):

active ingredient	10 mg
lactose	250 mg
starch	120 mg
magnesium stearate	5 mg

Tablets containing (per tablet):

active ingredient	10 mg
avicel	108 mg
colloidal silica	10 mg
talc	20 mg
magnesium stearate	2 mg

Injection solution (per 100 ml):

active ingredient	1000 mg
metagin	100 mg
NaCl	700 mg
HCl 0.1 N to pH 3.5	
Aq. sterilisata ad	100 ml

A therapeutically effective amount, expressed in mg per day, of the substance defined above, for instance amperozide, for use in the treatment of substance abuse disorders, would be from about 0.1 to about 40 mg, preferrably 0.1 to 20 mg, and especially 1-20 mg, depending on the specific condition to be treated, the age and weight of the specific patient and the specific patient's response to the medication. The exact individual dosage, as well as the daily dosage, will accordingly be determined according to standard medical principles under the direction of a physician. The animal tests referred to below have indicated that administration twice a day gives a therapeutical effect, and this would be expected to be the case also when the substance is administered to a human being.

The active ingredient may accordingly be expected to be administered to a patient in need of such treatment according to usual routes of administration and in usual forms. These include solutions, suspensions, emulsions, tablets, capsules, and powders prepared in pharmaceutically acceptable carriers for oral administration or sterile solution for parenteral administration.

In one embodiment of the invention the daily dose of the active substance is administered continuosly at a substantially constant level, over a given time period, for instance by an injection port or pump.

Various additives to enhance the stability or ease of administration of the drug are contemplated. The pharmaceutical composition may also contain additional therapeutically useful substances other than the pharmacologically active compounds of this invention for combination treatment.

Twenty years of research has consistently demonstrated that drugs that are abused by man are usually self-administered by laboratory animals. Ethanol, amphetamine, barbiturates,

benzodiazepines, cocaine, nicotine opioids, and phencyclidine and the like are just a few examples of substances abused by man and self-administered in animal models. The value of animal models for investigating the pharmacological and behavioural mechanisms underlying drug dependence has been repeatedly demonstrated. In fact, the animal models are our only recourse for the investigation of compounds to ameliorate or modify drug-seeking behaviour. In relation to this there is considerable experimental evidence supporting that a commonalty in the mechanism of the addictive process itself exists in the brain stem which underlies the predilection to abuse the above mentioned drugs.

The following examples are intended to illustrate the present invention without in any way limiting the scope thereof:

Example 1. Preparation of an amperozide tablet.

Amperozide tablets were prepared having the following composition:

Amperozide hydrochloride	5.0 mg
Lactose	105.5 mg
Microcrystalline cellulose	13.0 mg
Sodium Starch Glycolate	5.2 mg
Silicone Dioxide	0.65 mg
Magnesium Stearate	0.65 mg

The core composition was coated with a conventional sucrose coating to give a tablet for oral use.

Example 2. The effect of amperozide on cyanamide-induced alcohol drinking in rats.

The effect of amperozide administered systemically was determined in Spraque-Dawley rats induced to drink alcohol chronically by a series of intraperitoneal injections of cyanamide according to experimental procedures described previously (Critcher E.C. and Myers R.D., Alcohol 4:347-353,

1987). Intake of food and water and measures of body weight gain were recorded.

Amperozide given subcutaneously in a dose of 2.5 mg/kg b.i.d. over a three-day interval markedly altered the volitional consumption of alcohol. An immediate effect occurred following the administration of amperozide in terms of both absolute amount in g/kg and proportion of alcohol to water. The mean g/kg intake was reduced (P less than .01) by about 60% from the pretest level 4.4 g/kg to 1.6 g/kg of alcohol. The proportion of alcohol to total fluid consumed was similarly reduced from the pretest level. Of special importance is the fact that there were no significant effects produced by amperozide in terms of a change in the body weight or in the amounts of food and water consumed by the rats during the treatment period in comparison with the pretest level, demonstrating a pharmacological specificity of action of this drug.

Particularly notable is the finding that amperozide administered in a steady state dose regimen by an Alzet osmotic minipump implanted in the intrascapular space in a dose of 5 mg/kg/day for seven days attenuated significantly alcohol drinking in the cyanamide-treated rat in terms of both absolute g/kg and proportion of alcohol to water. In respect of the absolute intake of alcohol, the mean g/kg ingested decreased (P less than .01) from 7.0 g/kg to 3.4 g/kg of alcohol during the delivery of amperozide. In the four-day period following the systemically administered amperozide, i.e. after the minipump was depleted of the drug, the absolute g/kg intake of the rats was still suppressed. Moreover when the preference pattern was retested at 30, 70, 110 and 140 day intervals following the cessation of amperozide delivery the decline persisted. Concurrent with the effect on alcohol drinking, the consumption of food as well as level of body weight was unaffected by amperozide. These results with amperozide provide the first demonstration of an enduring action of any drug on aberrant alcohol drinking and clearly demonstrate that the actual compounds are useful for

preventing or reducing dependency on dependency-inducing agents.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

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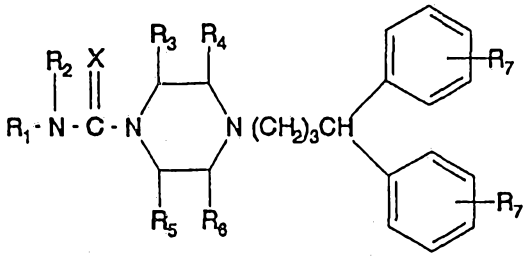
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method for the relief or prevention of a withdrawal syndrome resulting from addiction to a drug or substance of abuse and/or for the suppression of dependence on drugs or substances of abuse which comprises administering an effective amount of a diphenylbutyl-piperazinecarboxamide of the formula



wherein
R_1 and R_2 are groups independently selected from the group of H, alkyl chains, straight or branched, with 1-10 carbon atoms, cycloalkyl with 3-8 carbon atoms, aralkyl with 7-9 carbon atoms, alkenyl with 2-10 carbon atoms, phenyl unsubstituted or substituted by one to three groups selected from halogen, especially F, Cl and Br, lower alkyl with 1-5 carbon atoms, lower alkoxy with 1-5 carbon atoms, amine unsubstituted or substituted by one or two lower alkyl groups with 1-5 carbon atoms, $-CF_3$ and -CN groups,
R_3, R_4, R_5 and R_6 are groups independently selected from H, lower alkyl having from 1-3 carbon atoms and phenyl,
R_7 is selected from hydrogen, halogen especially F, Cl and Br, lower alkoxy with 1-3 carbon atoms and $-CF_3$, and
X is O or S,
or a physiologically acceptable salt thereof,
to a person in need of such treatment.

2. A method according to claim 1 wherein
R_1 is methyl, ethyl or n-, iso- or cyclopropyl,
R_2 is H,
R_3, R_4, R_5 and R_6 are hydrogen or R_3 and R_6 are hydrogen and

AUSTRALIAN PATENT OFFICE

R_4 and R_5 are methyl, or R_4 and R_5 are hydrogen and R_3 and R_6 are methyl,
R_7 is hydrogen or halogen, preferably one substituent on each benzene ring being F, and
X is O.

3. A method according to claim 1 or claim 2, wherein the diphenylbutyl-piperazinecarboxamide is amperozide, 4-[4,4-bis(4-fluorophenyl)butyl]-N-ethyl-1-piperazinecarboxamide or a physiologically acceptable salt thereof.

4. A method according to any one of the preceding claims, wherein the amperozide is administered in a daily dose of from 0.1 to 40 mg.

5. A method for the relief or prevention of a withdrawal syndrome resulting from addiction to a drug or substance of abuse and/or for the suppression of dependence on drugs or substances of abuse, substantially as hereinbefore described with reference to the Examples.

DATED this 15th day of August, 1994
Kabi Pharmacia AB
By Its Patent Attorneys
DAVIES COLLISON CAVE

AUSTRALIAN PATENT OFFICE

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE 92/00182

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

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

IPC5: A 61 K 31/495, C 07 D 295/215

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	A 61 K; C 07 D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in Fields Searched[8]

SE,DK,FI,NO classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	LIFE SCIENCES, Vol. 47, 1990 Eva Eriksson: "Amperozide,a putative anti-psychotic drug: uptake inhibition and release of dopamine in vitro in the rat brain", pp 2111-2117, see especially page 2116 --	1-4
X	US, A, 4308387 (BJÖRK ET AL) 29 December 1981, see column 8, example 5; column 5-6, Table I, compound II --	4
X	US, A, 4447433 (BJÖRK ET AL) 8 May 1984, see column 13, example 5; column 9-10, Table I-VII, compound II; the claims --	4
X	PHARMACOLOGY & TOXICOLOGY SUPPLEMENT, Vol. 1, 1990 J. Svartengren et al: "Receptor binding properties of amperozide", pp 8-11 --	4

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* Special categories of cited documents:[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document 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

"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

"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

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
29th June 1992	1992 -07- 0 2
International Searching Authority	**Signature of Authorized Officer**
SWEDISH PATENT OFFICE	Carolina Gomez Lagerlöf Carolina Gomez Lagerlöf

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

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 5-8, because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

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 [2]

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 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 additonal fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional seach fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/SE 92/00182

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 Swedish Patent Office EDP file on 29/05/92
The Swedish Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A- 4308387	81-12-29	AT-B-	376666	84-12-27
		AU-B-	529260	83-06-02
		AU-D-	5198479	80-06-19
		BE-A-	879528	80-04-21
		CA-A-	1130807	82-08-31
		CH-A-	643247	84-05-30
		DE-A-C-	2941880	80-04-30
		FR-A-B-	2439187	80-05-16
		GB-A-B-	2037745	80-07-16
		JP-C-	1482061	89-02-27
		JP-A-	55057572	80-04-28
		JP-B-	63026756	88-05-31
		LU-A-	81807	80-01-25
		NL-A-	7907741	80-04-22
		SE-B-C-	448730	87-03-16
		SE-A-	7908701	80-04-21
		US-A-	4385057	83-05-24
		US-A-	4447433	84-05-08
US-A- 4447433	84-05-08	AT-B-	376666	84-12-27
		AU-B-	529260	83-06-02
		AU-D-	5198479	80-06-19
		BE-A-	879528	80-04-21
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		CH-A-	643247	84-05-30
		DE-A-C-	2941880	80-04-30
		FR-A-B-	2439187	80-05-16
		GB-A-B-	2037745	80-07-16
		JP-C-	1482061	89-02-27
		JP-A-	55057572	80-04-28
		JP-B-	63026756	88-05-31
		LU-A-	81807	80-01-25
		NL-A-	7907741	80-04-22
		SE-B-C-	448730	87-03-16
		SE-A-	7908701	80-04-21
		US-A-	4308387	81-12-29
		US-A-	4385057	83-05-24