669327

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Section 29 (1)
Regulation 3.1 (2)

AUSTRALIA

Patents Act 1990

NOTICE OF ENTITLEMENT

We, **DR. MED MARIKA EHRLICH** of Bahnhofstraße 1, D-6509 Framersheim, Germany, and **PROFESSOR DR. HERBERT KUHL**, Hotzelstraße 18, D8750 Aschaffenburg, Germany, being the applicants / nominated person in respect of Application No. 11910/92 state the following:-

The Persons nominated for the grant of the patent are the actual inventors.

☐ The persons nominated for the grant of the patent are the applicants of the applications listed in the declaration under Article 8 of the PCT.

☐ The basic application listed on the request form is the first application made in a Convention country in respect of the invention.

DR. MED MARIKA EHRLICH and
PROFESSOR DR. HERBERT KUHL
By our Patent Attorneys,
WATERMARK PATENT & TRADEMARK ATTORNEYS

.....
Ian A. Scott
Registered Patent Attorney

4 April 1996
.....
(Date)

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(12) PATENT ABRIDGMENT (11) Document No. AU-B-11910/92
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 669327

(54) Title
OVULATION-PREVENTING AGENT FOR HORMONAL CONTRACEPTION

International Patent Classification(s)
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(57) Claim

1. A method of hormonal contraception, comprising the step of:

administering to a woman an ovulation-inhibiting preparation comprising:

two hormone constituents packed spatially separate in a packing unit intended for chronological, sequential oral administration, said constituents each comprising a plurality of daily hormone units accommodated spatially separate and individually removable in the packing unit.

wherein a first hormone constituent consists essentially of an oestrogen preparation which effects a disturbance of the follicle stimulation, and a second hormone constituent consists of an oestrogen preparation and a gestagen preparation in a dosage at least adequate to inhibit ovulation;

the first daily hormone unit of the first hormone constituent of the following cycle is administered on the day following the administration of the last of the daily units of the second hormone constituent of the current cycle, whereby a daily hormone unit is ingested every day; and

wherein the total number of daily hormone units is equal to 28.

(51) Internationale Patentklassifikation 5 :
A61K 31/57 // (A61K 31/57 A61K 31:565)

A1

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Veröffentlicht
Mit internationalem Recherchenbericht.

(54) Title: OVULATION-PREVENTING AGENT FOR HORMONAL CONTRACEPTION

(54) Bezeichnung: OVULATIONSHEMMENDES MITTEL ZUR HORMONALEN KONTRAZEPTION

(57) Abstract

An ovulation-preventing agent for hormonal contraception with two hormone components spatially separated in a packaging unit and intended for oral administration in a time sequence consisting of a number of spatially separated, individually removable daily hormone units placed in the packaging unit, whereby a first hormone component contains, as the active hormonal agent, essentially solely an oestrogen preparation interfering with the maturing of the follicle, while the second hormone component contains in combination an oestrogen preparation and a gestagen preparation in at least a sufficient quantity to prevent ovulation, in which the total number of the daily hormone units is the same as the total number of days of the desired cycle, the first hormone component comprises 5 to 14 and the second 23 to 14 daily units, and the number of daily units of the first hormone component is smaller than that of the second.

(57) Zusammenfassung

Ovulationshemmendes Mittel zur hormonalen Kontrazeption, mit zwei in einer Verpackungseinheit räumlich getrennt konfektionierten, zur zeitlich sequentiellen oralen Verabreichung bestimmten Hormonkomponenten, die jeweils aus einer Anzahl räumlich getrennt und einzeln entnehmbar in der Verpackungseinheit untergebrachter Hormon-Tageseinheiten bestehen, wobei eine erste der Hormonkomponenten als hormonellen Wirkstoff im wesentlichen ausschließlich ein eine Störung der Follikelreifung bewirkendes Östrogenpräparat, die zweite Hormonkomponente hingegen in Kombination ein Östrogen- und in mindestens zur Ovulationshemmung ausreichender Dosierung ein Gestagenpräparat enthält, dadurch gekennzeichnet, daß die Gesamtzahl der Hormon-Tageseinheiten gleich der Gesamtzahl der Tage des gewünschten Zyklus ist; daß die erste Hormonkomponente 5 bis 14 und die zweite Hormonkomponente 23 bis 14 Tageseinheiten umfaßt; und daß die Anzahl der Tageseinheiten der ersten Hormonkomponente geringer als die Anzahl der Tageseinheiten der zweiten Hormonkomponente ist.

OVULATION-INHIBITING MEANS FOR HORMONAL CONTRACEPTION

The invention is directed to an ovulation-inhibiting means for hormonal contraception, comprising two hormone constituents packed spatially separate in a packaging unit for chronologically sequential, oral administration that are each respectively composed of a plurality of daily hormone units accommodated spatially separated and individually removable in the packaging unit, whereby a first of the hormone constituents contains essentially only an estrogen preparation as hormonal agent effecting a disturbance of the follicle stimulation whereas the second hormone constituent contains an estrogen preparation and a gestagen preparation in a dose at least adequate to inhibit ovulation in combination.

Combination preparations, on the one hand, and, on the other hand, sequential preparations are known as hormonal ovulation inhibitors to be orally administered in daily units. In known combination preparations, for example, a combination of an estrogen preparation and of a gestagen preparation is administered for 21 days in constant or alternating, or absolute and/or relative dosing insofar as the desired cycle duration amounts to 28 days, whereby the estrogen preparation, for example, can be a natural estrogen or a synthetic ethinyl estradiol, and whereby the administration of the afore-mentioned 21 daily units is followed by a 7-day pause wherein a withdrawal bleeding simulating the natural menses occurs.

Again given a desired cycle duration of 28 days, a pure estrogen preparation is administered in the known sequential preparations for 7 days and the combination of an estrogen preparation and of a gestagen preparation is then administered for 15 days, whereby an administration-free time of, for example, six days again follows here, the withdrawal bleeding occurring during this period. Although it is in fact already known to bridge the administration pause inherent in the combination and in the sequential preparations for the sake of a greater reliability of

administration in that placebos are administered during the appertaining days, it was nonetheless hitherto previously assumed that no hormones of the type under discussion here dare be administered during the approximately one-week administration pause in order to guarantee a reliable withdrawal bleeding. Only in substitution preparations were hormones administered over the entire cycle, for example in the sequence of 10 days of estrogen preparation, 11 days of a combination of estrogen and gestagen preparation, 7 days of estrogen preparation in an especially low dose; these substitution preparations, however, are not suitable for inhibiting ovulation.

The sequential preparations employed in substitution therapy are unsuitable for contraception, particularly because the natural estradiol does not prevent ovulation in the given dose and the phase during which gestagen is administered is too short, being only 11 days long. The sequential arrangement set forth above, however, does guarantee a relatively good cycle control in the case of the substitution of preparations.

In general, the three most important aspects that are to be taken into consideration in hormonal contraception are the contraceptive reliability, a good cycle control as well as a minimum of side-effects. The contraceptive reliability is mainly based on the action of the gestagen constituent; in a known preparation, it is utilized in a dose that is approximately twice as high as the dose necessary for inhibiting ovulation. Added thereto are the peripheral effects of the gestagen on cervix, fallopian tubes and endometrium. Consequently, gestagen is present in an adequate dose in modern oral contraceptives in order to guarantee a reliable contraception. The synthetic estrogen, ethinyl estradiol, normally employed thereby additionally intensifies the ovulation-inhibiting effect of the gestagen. Combined ethinyl estradiol-gestagen preparations that are taken

over three of four weeks with an administration pause of 7 days have hitherto shown the greatest contraceptive reliability. The sequential preparations are somewhat less reliable in view of the contraception reliability since 50µg ethinyl estradiol are administered during the pure estrogen phase lasting, for example, 7 days, this not preventing ovulation in all women and also lacking the peripheral contraceptive effects of the gestagen. The ovulation-inhibiting dose (100% of women) of ethinyl estradiol, namely, amounts to 100µg daily.

Whereas the combination preparations as recited above offer the greatest contraceptive reliability among known ovulation inhibitors, the best cycle control, (regular withdrawal menses optimally few intermenses) is established given the employment of sequential preparations, including those of the species that - similar to a normal ovulatory cycle - effect proliferation of the endometrium due to a 7-day action of the estrogen (unimpeded by gestagen) before the gestagen added, for example, beginning with the eighth day inhibits further proliferation and secretionally converts the endometrium. As already presented, a menstruation-like withdrawal bleeding occurs approximately 2 through 3 days after the last estrogen-gestagen tablet, whereas the proliferation of the endometrium is reduced from the very outset given employment of the combination preparations, so that the cycle control in the latter case is poorer than in the case of the sequential preparations.

Particularly given employment of ethinyl estradiol as estrogen constituent in sequential preparations, it has been shown that higher doses are necessary, particularly during the initial phase, in order to guarantee the contraceptive effectiveness; this, however, in turn harbors the risk of serious and dangerous complications or, respectively, side-effects (thromboembolism). The gestagen thus employed can even intensify this effect in some

cases, whereby the risk increases with increasing age and is especially pronounced in the case of women at an age of more than 40 years. A fundamental solution would be the employment of combination preparations that contain the natural estrogen, estradiol, instead of ethinyl estradiol since it is known from experience with substitution therapy and post-menopausal women that treatment with estradiol involves substantially fewer health risks; however, estradiol is hardly suitable for employment in combination preparations. The gestagen constituent thereby in fact guarantees a reliable contraception; since, however, gestagen causes an intensified inactivation of the estradiol in the endometrium due to stimulation of local enzymes and the estrogen effect on the endometrium is greatly reduced, intermenses frequently occur involving the disadvantageous effects already set forth. By contrast thereto, ethinyl estradiol is metabolized far more slowly in the endometrium and, consequently, has an adequate effect on the endometrium.

U.S. Patent No. 4,921,843 discloses an ovulation-inhibiting means of the species, whereby an administration pause of at least one day that, for example, can be bridged with a placebo is provided between the administration of the last of the daily hormone units such as dragees, tablets, or the like of the second hormone constituent before the new daily hormone unit, namely the first of the first hormone constituent of the following cycle, is administered. This is in agreement with the previously prevailing opening of the field in court wherewith, namely, an administration pause of at least one day or, on the other hand, a drastic reduction in the effective estrogen level was considered absolutely necessary in order to trigger a withdrawal bleeding. Even when a one-day administration pause is involved, however, such a discontinuation of the estrogen leads to modifications in circulation that, for example, can cause headaches (migrane

attacks) and also leads to brief-duration changes in various metabolism parameters, particularly hemostasis so that a stable metabolism situation is out of equilibrium for one or more days in view of the estrogen influence.

In the means for treating climacteric failure phenomena disclosed by German published application 26 45 307, an administration pause or at least the simulation of an administration pause on the basis of temporary employment of an especially weak type of estrogen that, differing from the means of the species, does not effect any adequate disturbance of the follicle stimulation is considered necessary. Overall, the hormone doses thereby employed, particularly the duration of the gestagen phase, are thereby inadequate for contraception given the means disclosed in the afore-mentioned publication. German published application 24 31 704 likewise discloses a means for alleviating climacteric complaints wherein fluctuating estrogen concentrations are provided. The gestagen doses thereby only begin after the middle of the cycle, for which reason a contraceptive effect cannot be achieved. Moreover, a hormone-free pause in administration is absolutely prescribed.

European Published Application 0 368 373 discloses an ovulation-inhibiting means, whereby a constant gestagen level is provided over the entire cycle duration, estrogen phases being cyclically superimposed thereon. What is thereby disadvantageous is that there is an increased risk of intermenses and that the lasting gestagen administration in fact has a good contraceptive effect but also involves a lasting, blood vessel-constricting effect, so that negative influences on health cannot be excluded, precisely in the case of women having a tendency to circulatory problems, for instance with increasing age.

The object of the invention is to improve the ovulation-inhibiting means of the species to the effect that, given high

contractive reliability, a faultless cycle control is achieved while reliably avoiding intermenses and side-effects are avoided.

This object is inventively achieved in that the total number of daily hormone units is equal to the total number of days in the desired cycle; in that the first hormone constituent covers 5 through 14 daily units and the second hormone constituent covers 23 through 14 daily units; and in that the plurality of daily units of the first hormone constituent is lower than the plurality of daily units of the second hormone constituent.

It can thereby be provided that at least one of the estrogen preparations comprises at least one constituent from the group covering hormone compounds that quickly split off ethinyl estradiol, mestranol, other synthetic estrogens as well as at least one of the afore-mentioned hormone constituents after being ingested.

A further embodiment of the invention is characterized in that at least one of the estrogen preparations comprises at least one constituent from the group covering hormone compounds that quickly split off estradiol, estrone and/or other natural estrogens as well as at least one of the afore-mentioned hormone constituents after ingestion.

It can also be provided in the invention that the gestagen preparation comprises at least one constituent from the group covering hormone compounds that quickly split off progesterone, chlormadinon acetate, norethindrone acetate, cyproterone acetate, desogestrel, levonorgestrel, other natural and/or synthetic gestagens as well as at least one of the afore-mentioned hormone constituents after ingestion.

The invention also proposes that the total number of daily units amounts to 28.

It can also be provided in the invention that the first hormone constituent covers at most 10 daily units.

A further embodiment of the invention is characterized in that the first hormone constituent covers 7 daily units and the second hormone constituent covers 21 daily units.

It can also be provided in the invention that the number of daily units is adapted to the natural, individual cycle of the woman.

The invention is based on the surprising perception that one succeeds in improving the contraceptive reliability as well as the cycle control in that, first, a hormonal control of the follicular action over the entire cycle is guaranteed, first, by an early disturbance of the follicle stimulation within the hitherto standard hormonal administration pause, namely on the basis of the estrogen constituent to be then taken. In that an adequate build up of mucus membrane first occurs in the pure estrogen phase similar to the conditions naturally occurring, on the other hand, intermenses occur far more rarely even given a lower dosage of the hormone constituents in the actual ovulation-inhibiting phase wherein a combination of estrogen and gestagen is administered. The pure estrogen phase amounts to at least five days and can be extended up to 10 days when natural estrogen is employed and can be extended up to 14 days when synthetic estrogen is employed, this then being followed by the generally longer combined phase, dependent on the desired cycle duration.

As constitutes the subject matter of a specific embodiment of the invention, it is especially advantageous when the number of daily units of the inventive means is matched to the natural, individual cycle of the pertinent woman since an especially beneficial condition is then achieved with reference to avoiding undesired side-effects.

The pure estrogen phase at the beginning of the inventive treatment enables an adequate proliferation of the endometrium. A reliable contraceptive protection is particularly achieved when,

as inventively preferably proposed, the gestagen in the following combination phase is administered in twice the ovulation-inhibiting dose in the individual daily units. After taking the last of the gestagen-containing tablets, withdrawal bleeding occurs within a few days during the next-following estrogen phase, whereby a renewed proliferation of the endometrium is simultaneously stimulated due to the ingestion of the estrogen. In view of the health risk, it is particularly that embodiment of the invention wherein only natural estrogen is employed that is of great advantage since especially low side-effects can be anticipated here given adequate contraceptive reliability and cycle control.

The ovulation-inhibiting means of the invention is utilized such that a defined number of daily hormone units such as dragees, tablets or the like of the first hormone constituent that essentially contains only an estrogen preparation as hormonal agent are orally administered on successive days for hormonal contraception within the desired cycle and that, following thereupon, [a defined plurality of daily hormone units such as dragees, tablets or the like] of the second hormone constituent that contains an estrogen preparation and a gestagen preparation in a dose at least adequate for inhibiting ovulation in combination are orally administered, whereby the first of the daily units of the first hormone constituent of the following cycle is administered the day following the administration of the last of the daily units of the second hormone constituent of the appertaining cycle, so that a daily hormone unit is ingested every day, eliminating administration pauses.

The bleeding occurring given the employment of the ovulation-inhibiting means of the invention involves less blood loss and is less painful, due to the continuing estrogen administration than in the case of the ovulation-inhibiting means of the prior art from which the invention departs as species. The contraceptive

reliability is also noticeably higher because there are no administration-free days, not even a single day on which the contraceptive reliability could otherwise be overcome as a result of natural hormonal processes. Due to the lasting estrogen administration, moreover, a definitely positive, vessel-expanding effect arises, circulatory problems being thereby capable of being opposed. A further advantage of the ovulation-inhibiting means of the invention is comprised therein is that is what is referred to as the pre-menstrual syndrome is suppressed given employment thereof; this can disadvantageously occur as in the course of a natural cycle given discontinuation of the estrogen for only one day or for only a few days.

The uniform estrogen level that is achieved given employment of the ovulation-inhibiting means of the invention also avoids the decrease following rise of coagulation parameters during the hormone-free days or, respectively, after the restoration of administration in the next cycle, as a result whereof, among other things, the coagulation system situated in a stable equilibrium would otherwise be disturbed. The ovulation inhibiting means of the invention is therefore also particularly suitable for women over the age of 40; as known, the risk of circulation problems increases in this age group with increasing age.

The invention also covers a method for hormonal contraception that is comprised in the prescribed administration of the ovulation-inhibiting means according to the patent claims, whereby a contraceptively active estrogen dose is thereby administered interruption-free, gestagen doses being cyclically superimposed thereon.

The invention shall be set forth in detail below with reference to exemplary embodiments.

Example 1:

A sequential preparation that contained 7 daily units each having respectively 4 mg estradiol as well as 21 daily units each having respectively 4 mg estradiol and 1 mg norethindrone acetate was employed for ovulation-inhibiting treatment. The means was administered for a period of one year and exhibited practically no side-effects given an extremely good contraceptive reliability, whereby intermenses occurred far more rarely than in the case of traditional low-dosage preparations.

Example 2:

An ovulation-inhibiting means in the form of a sequential preparation comprising 7 daily units each having respectively 2 mg estradiol valerate and 21 daily units each having respectively 4 mg estradiol valerate and 2 mg chlormadinone acetate was employed for hormonal contraception. The effectiveness corresponded to that of Example 1.

Example 3:

An ovulation-inhibiting means was employed that contained 10 daily units each having respectively 20µg ethinyl estradiol and 18 daily units each having respectively 20µg ethinyl estradiol and 150µg levonorgestrel. The observations during administration corresponded to those of Example 1 and of Example 2.

Both individually as well as in arbitrary combination, the features of the invention disclosed from the above specification and in the claims can be critical for realizing the various embodiments of the invention.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

~~10. A preparation according to any one of the previous claims, characterised by a dosage of the hormonal components such that when the agent is used a uniform oestrogen level is obtainable.~~

1. A method of hormonal contraception, comprising the step of:

administering to a woman an ovulation-inhibiting preparation comprising:

two hormone constituents packed spatially separate in a packing unit intended for chronological, sequential oral administration, said constituents each comprising a plurality of daily hormone units accommodated spatially separate and individually removable in the packing unit.

wherein a first hormone constituent consists essentially of an oestrogen preparation which effects a disturbance of the follicle stimulation, and a second hormone constituent consists of an oestrogen preparation and a gestagen preparation in a dosage at least adequate to inhibit ovulation;

the first daily hormone unit of the first hormone constituent of the following cycle is administered on the day following the administration of the last of the daily units of the second hormone constituent of the current cycle, whereby a daily hormone unit is ingested every day; and

wherein the total number of daily hormone units is equal to 28.

2. The method of claim 11, wherein at least one of the oestrogen preparations comprises at least one hormone constituent from the group of hormones that quickly splits off ethinyl estradiol, mestranol, and other synthetic oestrogens as well as at least one of the aforementioned hormone constituents after ingestion.

3. The method of claim 11, wherein at least one of the oestrogen preparations comprises at least one hormone constituent from the group of hormones that quickly splits off estradiol, estrone, or other natural oestrogens as well as at least one of the aforementioned hormone constituents after ingestion.

4. The method of claim 11, wherein the gestagen preparation comprises at least one hormone constituent from the group of hormones that quickly splits off progesterone, chloromadinone acetate, norethisterone acetate, cyproterone acetate, desogestrel, levonorgestrel, or other natural or synthetic gestagens as well as at least one of the aforementioned hormone constituents after ingestion.

5. The method of claim 11, wherein the first hormone constituent comprises a maximum of 10 daily units.

6. The method of claim 11, wherein the first hormone constituent comprises 7 daily units and the second hormone constituent comprises 21 daily units.

7. The method of claim 11, wherein the number of daily units corresponds to the natural cycle of a woman.

DATED this 28th day of March, 1996.

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IAS:SI:JL VAX doc 07 AU1191092.WPC

Abstract

Ovulation-inhibiting means for hormonal contraception, comprising two hormone constituents packed spatially separate in a packing unit intended for chronological sequential, oral administration, each thereof being composed of a plurality of daily hormone units accommodated spatially separate and individually removable in the packaging unit, whereby a first of said hormone constituents contains essentially only an estrogen preparation effecting a disturbance of the follicle stimulation as hormonal agent but the second hormone constituent contains an estrogen preparation and a gestagen preparation at least in a dose adequate for inhibiting ovulation, characterized in that the total number of daily hormone units is equal to the total number of days in the desired cycle; in that the first hormone constituent covers 5 through 14 daily units and the second hormone constituent covers 23 through 14 daily units; and in that the number of daily units of the first hormone constituent is lower than the number of daily units of the second hormone constituent.

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen PCT/DE 92/00081

I. KLASSIFIKATION DES ANMELDUNGSGEGENSTANDS (bei mehreren Klassifikationssymbolen sind alle anzugeben)[6]

Nach der Internatiooalen Patentklassifikation (IPC) oder nach der nationalen Klassifikation und der IPC

Int.Cl.5 A 61 K 31/57 //(A 61 K 31/57 A 61 K 31:565)

II. RECHERCHIERTE SACHGEBIETE

Recherchierter Mindestprüfstoff [7]

Klassifikationssytem	Klassifikationssymbole
Int.Cl.5	A 61 K

Recherchierte nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Sachgebiete fallen [8]

III. EINSCHLAGIGE VEROFFENTLICHUNGEN [9]

Art.°	Kennzeichnung der Veröffentlichung [11], soweit erforderlich unter Angabe der maßgeblichen Teile [12]	Betr. Anspruch Nr.[13]
A	EP,A,0368373 (AKZO N.V.) 16. Mai 1990, siehe Zusammenfassung (in der Anmeldung erwähnt) ---	1-8
A	EP,A,0036229 (AKZO N.V.) 23. September 1981, siehe Zusammenfassung -----	1-8

° Besondere Kategorien von angegebenen Veröffentlichungen [10] :

"A" Veröffentlichung, die den allgemeinen Stand der Technik definiert, aber nicht als besonders bedeutsam anzusehen ist

"E" älteres Dokument, das jedoch erst am oder nach dem internationalen Anmeldedatum veröffentlicht worden ist

"L" Veröffentlichung, die geeignet ist, einen Prioritätsanspruch zweifelhaft erscheinen zu lassen, oder durch die das Veröffentlichungsdatum einer anderen im Recherchenbericht genannten Veröffentlichung belegt werden soll oder die aus einem anderen besonderen Grund angegeben ist (wie ausgeführt)

"O" Veröffentlichung, die sich auf eine mündliche Offenbarung, eine Benutzung, eine Ausstellung oder andere Maßnahmen bezieht

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"X" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann nicht als neu oder auf erfinderischer Tätigkeit beruhend betrachtet werden

"Y" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann nicht als auf erfinderischer Tätigkeit beruhend betrachtet werden, wenn die Veröffentlichung mit einer oder mehreren anderen Veröffentlichungen dieser Kategorie in Verbindung gebracht wird und diese Verbindung für einen Fachmann naheliegend ist

"&" Veröffentlichung, die Mitglied derselben Patentfamilie ist

IV. BESCHEINIGUNG

Datum des Abschlusses der internationalen Recherche	Absendedatum des internationalen Recherchenberichts
06-05-1992	27. 05. 92
Internationale Recherchenbehörde	**Unterschrift des bevollmächtigten Bediensteten**
EUROPAISCHES PATENTAMT	Nicole De Bie

Formblatt PCT/ISA/210 (Blatt 2) (Januar 1985)

ANHANG ZUM INTERNATIONALEN RECHERCHENBERICHT ÜBER DIE INTERNATIONALE PATENTANMELDUNG NR.

DE 9200081
SA 56095

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben.
Die Angaben über die Familienmitglieder entsprechen dem Stand der Datei des Europäischen Patentamts am 18/05/92
Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie		Datum der Veröffentlichung
EP-A- 0368373	16-05-90	AU-A-	4287989	26-04-90
		CA-A-	2000438	13-04-90
		JP-A-	2174717	06-07-90
EP-A- 0036229	23-09-81	NL-A-	8001593	16-10-81
		AT-T-	11371	15-02-85
		AU-B-	546010	08-08-85
		AU-A-	6821081	24-09-81
		CA-A-	1158981	20-12-83
		JP-B-	1053252	13-11-89
		JP-C-	1567547	10-07-90
		JP-A-	56140914	04-11-81
		US-A-	4378356	29-03-83

EPO FORM P0473

Für nähere Einzelheiten zu diesem Anhang : siehe Amtsblatt des Europäischen Patentamts, Nr.12/82

INTERNATIONAL SEARCH REPORT

International Application No PCT/DE 92/00081

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

Int.Cl. 5 A 61 K 31/57 //(A 61 K 31/57 A 61 K 31:565)

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
Int.Cl. 5	A 61 K

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

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]
A	EP,A,0368373 (AKZO N.V.) 16 May 1990 see abstract (cited in the application)	1-8
A	EP,A,0036229 (AKZO N.V.) 23 September 1981 see abstract	1-8

* 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
6 May 1992 (6.05.92)	27 May 1992 (27.05.92)
International Searching Authority	**Signature of Authorized Officer**
European Patent Office	

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. DE 9200081 SA 56095

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 18/05/92
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