Il concetto di *novelty* nell'ambito della protezione brevettuale come elemento di indirizzo della ricerca farmaceutica

Tesi di laurea pratico-professionale
in Farmacia

Presentata da
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A.A. 2014-2015

brevetto

European patents shall be granted for any inventions …

NOVELTY
inventive step
industrial application
ethics

Article 52 EPC 2000

novelty

not exclude the patentability of
any substance or composition for
any specific use

An invention shall be considered to be new
if it does not form part of the State of the art

1) new disease

2) new route of administration

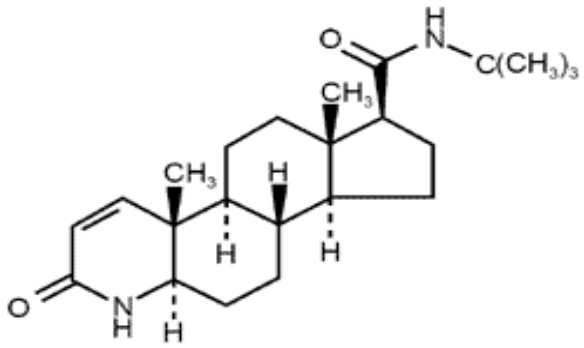
3) new type of patient

4) new dosing regimen

Article 54 EPC 2000

1) new disease

FINASTERIDE



Alopecia androgenetica

EP0724444

patent granted 06.08.1997

Ipertrofia prostatica benigna

US4760071

patent granted 26.06.1988

a different therapeutic use

T0031/96

back to room temperature. The Form II prepared in this manner has the same physical characterization data as given above.

EXAMPLE 3

Preparation of Human prostatic 5α-reductase.

Samples of human tissue were pulverized using a freezer mill and homogenized in 40 mM potassium phosphate, pH 6.5, 5 mM magnesium sulfate, 25 mM potassium chloride, 1 mM phenylmethylsulfonyl fluoride, 1 mM dithiothreitol (DTT) containing 0.25 M sucrose using a Potter-Elvehjem homogenizer. A crude nuclear pellet was prepared by centrifugation of the homogenate at 1,500xg for 15 min. The crude nuclear pellet was washed two times and resuspended in two volumes of buffer. Glycerol was added to the resuspended pellet to a final concentration of 20%. The enzyme suspension was frozen in aliquots at -80°C. The prostatic reductases were stable for at least 4 months when stored under these conditions.

5α-reductase assay

The reaction mixture for the type 2 5α-reductase contained 40 mM sodium citrate, pH 5.5, 0.3 μM [7-^{3}H]-testosterone, 1 mM dithiothreitol and 500 μM NADPH in a final volume of 100 μl. Typically, the assay was initiated by the addition of 50-100 μg prostatic homogenate and incubated at 37°C. After 10-50 min the reaction was quenched by extraction with 250 μl of a mixture of 70% cyclohexane: 30% ethyl acetate containing 10 μg each DHT and T. The aqueous and organic layers were separated by centrifugation at 14,000 rpm in an Eppendorf microfuge. The organic layer was subjected to normal phase HPLC (10 cm Whatman partisil 5 silica column equilibrated in 1 ml/min 70% cyclohexane: 30% ethyl acetate; retention times: DHT, 6.8-7.2 min; androstanediol, 7.6-8.0 min; T, 9.1-9.7 min). The HPLC system consisted of a Waters Model 680 Gradient System equipped with a Hitachi Model 655A autosampler, Applied Biosystems Model 757 variable UV detector, and a Radiomatic Model A120 radioactivity analyzer. The conversion of T to DHT was monitored using the radioactivity flow detector by mixing the HPLC effluent with one volume of Flo Scint 1 (Radiomatic). Under the conditions described, the production of DHT was linear for at least 25 min. The only steroids observed with the human prostate preparation were T, DHT and androstanediol.

Inhibition studies

Compounds were dissolved in 100% ethanol. IC_{50} values represent the concentration of inhibitor required to decrease enzyme activity to 50% of the control. IC_{50} values were determined using a 6 point titration where the concentration of the inhibitor was varied from 0.1 to 1000 nM.

EXAMPLE 4

Macrophotography And Global Photography Procedure For Detection Of Hair Growth

A. Macrophotographic Procedure

Location:	ID card Haircount target area
Equipment:	Film: Kodak-T-max 24 exposure each of same emulsion lot number
Camera:	Nikon N-6000
Lens:	Nikkor 60 mm f2.8
Flashes:	Nikon SB-21B Macroflash
Device:	registration device

Photographic Procedure:

In these clinical photographs, the only variable allowed is the haircount. Film emulsion, lighting, framing, exposure, and reproduction ratios are held constant.

1. The haircount area on the patient is prepared as follows: A small (~1mm) dot tattoo is placed at the beginning of the study at the leading edge of the bald area directly anterior to the center of the vertex bald spot, using a commercial tattooing machine or manually (needle and ink). An area approximately one square inch in size, centered at the tattoo at the leading edge of the balding area, is clipped short (~2mm). Cut hairs are removed from the area to be photographed, using tape. Compressed air and/or ethanol wipes may also be used to facilitate removal of cut hairs.

2. Magnification: Each lens supplied has a fixed reproduction ratio of 1:1.2.
Aperture: Every photograph is taken at f/22.
Film: T-Max 100 (24 exposure) is used.

3. Patient's haircount target area. Three exposures (-2/3, 0, and +2/3 f-stop).

A trained technician places a transparency over the photographic print and, using a felt tip pen, places a black dot over each visible hair. The dot map transparency is then counted using image analysis with computer assistance.

Photographs are coded with a random number corresponding to study site, visit number and patient allocation number to insure blinding to time. At Month 6, baseline and Month 6 photographs are counted and data analyzed for interim analysis. At Month 12, baseline, Month 6 and Month 12 photographs are counted and data analyzed for the primary endpoint.

Methodology for detection of hair growth is also

described in Olsen, E.A. and DeLong, E., *J. American Academy of Dermatology,* Vol. 23, p. *470* (**1990**).

B. Global Photographic Procedure

Locations:	Color card/patient Id Global photograph
Equipment:	Film: Kodachrome KR-64 24 exposure each of same emulsion lot number
Camera:	Nikon N-6000
Lens:	Nikkor 60 mm f2.8
Flashes:	Nikon SB-23

Photographic Procedure

In these clinical photographs, the only variable allowed is the global area's appearance. Anything extraneous to the area (clothing, furniture, walls, etc.) is eliminated from the fields to be photographed.

1. Patients will have global photographs taken prior to hair clipping with the head in a fixed position (determined by the supplied stereotactic device). Hair on the patient's head is positioned consistently so as to not obscure the bald area.

2. Magnification: Each lens supplied has a fixed reproduction ratio of 1:6.
Aperture: Every photograph will be taken at f/11.
Film: Kodachrome (24 exposure) is used.

3. Patient's global photographs. Three exposures at zero compensation.

Using the above-described methodology, it can be shown that administration of finasteride, in dosages per day per patient of, for example, 1 mg/day or 0.2 mg/day, are useful in the treatment of androgenic alopecia, and promote hair growth in patients with this condition.

EXAMPLE 5

In another test, finasteride was orally administered for 6 weeks to men with male pattern baldness at doses of 0.2 mg/day and 1.0 mg/day (and, for comparison, 5.0 mgs/day). The results of this test showed a significant reduction in DHT content in scalp tissue of the test participants.

Claims

1. The use of 17β-(N-tert-butylcarbamoyl)-4-aza-5-alpha-androst-1-ene-3-one for the preparation of a medicament for oral administration useful for the treatment of androgenic alopecia in a person and wherein the dosage amount is about 0.05 to 1.0 mg.

2. The use as claimed in claim 1 wherein the dosage is 1.0 mg.

3. The use as claimed in claim 1 or 2 wherein the treatment is of male pattern baldness.

Patentansprüche

1. Die Verwendung von 17β-(N-tert.-Butylcarbamoyl)-4-aza-5-alpha-androst-1-en-3-on zur Herstellung eines Medikaments zur oralen Verabreichung, das zur Behandlung von androgener Alopezie bei einer Person geeignet ist, und bei der die Dosismenge etwa 0,05 bis 1,0 mg beträgt.

2. Die wie in Anspruch 1 beanspruchte Verwendung, bei der die Dosis 1,0 mg beträgt.

3. Die wie in Anspruch 1 oder 2 beanspruchte Verwendung, bei der Alopezie des männlichen Typs behandelt wird.

Revendications

1. Utilisation de la 17 β (N-tert-butylcarbamoyl)-4-aza-5-alpha-andros-1-ène-3-one pour la préparation d'un médicament pour l'administration orale, utile pour le traitement de l'alopécie androgénique sur une personne et dans laquelle la quantité d'administration est d'environ 0,05 à 1,0 mg.

2. Utilisation selon la revendication 1, dans laquelle la posologie est de 1,0 mg.

3. Utilisation selon la revendication 1 ou 2, dans laquelle le traitement est celui de l'alopécie hippocratique.

2) new route of administration

HCG

Via sottocutanea

EP0290644

patent granted 15.11.1995

Via intramuscolo

Regmington's Pharmaceutical Sciences 1980

Sterilità

Disordini sessuali maschili

Pharmacokinetics study

Testosterone serum level (ng/ml) following i.m and s.c. injection of 5.000 IU HCG		
hours after injection	i.m.	s.c.
0	7.94 ± 2.31	7.74 ± 2.70
1	7.62 ± 2.17	7.56 ± 2.42
2	8.10 ± 2.01	8.78 ± 2.57
4	7.98 ± 2.10	9.46 ± 3.39
6	7.98 ± 1.91	8.69 ± 3.22
8	8.95 ± 1.99	9.87 ± 3.05
12	8.49 ± 2.07	10.06 ± 3.45
16	10.27 ± 2.24	10.72 ± 3.45
22	11.83 ± 2.97	11.98 ± 3.60
26	10.03 ± 2.32	11.66 ± 3.86
30	11.31 ± 3.53	11.78 ± 4.14
36	11.64 ± 3.34	12.44 ± 3.59
48	14.36 ± 3.74	13.77 ± 4.12
72	14.99 ± 3.99	14.18 ± 3.73
96	14.94 ± 3.64	13.91 ± 4.37
120	14.21 ± 3.65	13.30 ± 3.46
144	12.50 ± 2.83	12.08 ± 3.95

LH serum level (mU/ml) following i.m and s.c injection of 5.000 IU HCG		
hours after injection	i.m.	s.c.
0	4.00 ± 1.79	4.13 ± 1.17
1	3.70 ± 1.71	3.74 ± 0.99
2	3.34 ± 1.40	3.59 ± 1.26
4	3.39 ± 1.47	3.27 ± 1.14
6	3.01 ± 1.90	3.00 ± 0.98
8	3.42 ± 2.12	3.49 ± 1.21
12	2.37 ± 1.16	3.16 ± 1.21
16	2.49 ± 1.13	2.63 ± 1.15
22	2.01 ± 0.64	1.77 ± 0.83
26	1.54 ± 0.86	1.42 ± 0.39
30	1.79 ± 0.77	1.46 ± 0.73
36	1.56 ± 0.95	1.56 ± 0.59
48	1.41 ± 0.79	1.58 ± 0.79
72	1.53 ± 1.31	1.60 ± 0.94
96	1.71 ± 1.39	2.01 ± 2.21
120	1.05 ± 0.98	1.65 ± 2.17
144	0.91 ± 1.07	1.11 ± 1.01

FSH serum level (mU/ml) following i.m and s.c injection of 5.000 IU HCG		
hours after injection	i.m.	s.c.
0	4.03 ± 1.82	3.63 ± 2.61
4	3.79 ± 1.78	3.14 ± 2.33
12	3.43 ± 1.40	2.91 ± 2.02
22	2.99 ± 1.31	2.46 ± 1.82
48	2.02 ± 1.05	1.89 ± 1.54
72	1.69 ± 0.97	1.42 ± 1.47
96	1.62 ± 0.77	1.58 ± 1.83
120	1.21 ± 0.48	1.30 ± 1.64
144	1.02 ± 0.59	1.01 ± 1.51

new technical teaching

Miglioramento della compliance del paziente

Potenziale miglioramento dell'efficacia terapeutica

Riduzione delle complicanze legate alla via di somministrazione

Mantenimento degli stessi effetti biologici di HCG somministrato per via intramuscolo

EP0290644
patent granted …..
SERONO

T 0051/93

3) new type of patient

OMEGA-3

Post-infartuati
IT1235879
patent granted 23.11.1992 ?????

Persone sane
EP1152755
date of filling 07.02.2000 ???????

DISTURBI CARDIOVASCOLARI

therapeutic purpose

Riduzione di alcuni fattori di rischio
cardiovascolari in pazienti essenzialmente sani

Disturbi cardiovascolari

Prevenire la mortalità in pazienti sopravvissuti
ad un primo infarto miocardico

a different therapeutic use

EP1152755
patent not granted

RG n.21484/06

Alla luce del precedente brevetto IT'79 due CCTTU hanno dato parere positivo sulla validità del brevetto EP'55 riconoscendo nella diversa tipologia di paziente una nuova applicazione terapeutica.

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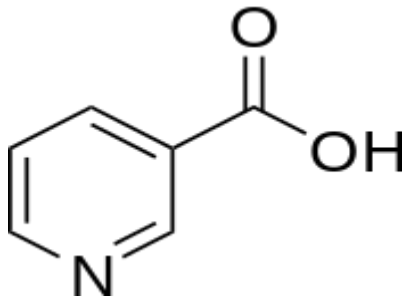
Il giudice responsabile del caso ha invece negato la validità dello stesso per mancanza di attività inventiva non rispetto il brevetto italiano, bensì rispetto al protocollo di studio (GISSI) utilizzato come guida per la conduzione dello studio clinico.

4) new dosing regimen

ACIDO NICOTINICO
(1500mg)



Una volta al giorno
prima di dormire
EP0643965
patent granted 22.04.2008

IPERLIPIDEMIA

Due volte al giorno
dopo i pasti
US5126145
patent granted 15.09.1998

4) new dosing regimen

Same dosage and different frequency of administration

Different dosage and same frequency of administration

Different dosage and a different frequency of administration

Clinical trial- Lipid Profile

Patient Study Lipid Profile Data

GROUP A

Pt. No.	Total-C	LDL-C	Apo B	Trigs	HDL-C	HDL_2-C	Lp(a)
1	-8.2	-12.0	NA	-17.3	22.0	NA	NA
2	-5.9	-27.0	NA	-28.7	65.0	NA	NA
3	-15.1	-13.0	NA	-22.0	-9.1	NA	NA
4	-3.3	-10.0	NA	61.6	3.8	NA	NA
5	-16.5	-17.7	NA	-28.8	11.1	NA	NA
6	-12.4	-25.9	NA	-42.0	51.6	NA	NA
7	-24.2	-31.4	NA	-39.4	12.5	NA	NA
8	-6.7	-7.4	NA	-42.4	18.8	NA	NA
9	4.5	1.1	NA	7.2	9.2	NA	NA
10	2.8	-0.2	NA	-2.7	22.9	NA	NA
11	-13.0	-9.4	NA	-54.0	44.3	NA	NA
Mean	-8.9	-13.9	NA	-18.9	23.0	NA	NA
p-Value	0.0004	0.0001		0.0371	0.0068		

GROUP B

1	-19.2	-27.1	-24.4	-33.4	20.0	22.3	-81.9
2	-32.2	-35.7	-28.0	-60.4	4.3	3.2	-25.3
3	-21.4	-33.6	-35.6	-33.4	30.4	38.6	-17.4
4	-19.9	-24.6	-15.1	-20.8	9.6	16.1	-27.0
5	-3.3	-2.1	-29.4	-41.1	5.8	2.4	-22.4
6	PATIENT WITHDREW FROM STUDY						
7	23.1	-32.6	-42.6	-58.6	49.2	68.9	-14.3
8	24.8	34.0	-28.4	5.5	6.5	-6.8	NA
9	10.1	12.0	-16.8	-11.6	20.7	-12.3	40.6
10	-2.9	-7.7	-28.0	-59.0	53.1	70.5	-41.2
11	-10.5	-18.8	-25.3	-53.4	31.8	39.7	NA
12	-20.0	-30.8	-30.4	11.7	21.1	25.0	-28.4
13	17.4	16.8	-17.5	-17.5	51.3	51.9	38.5
14	-9.4	-16.6	-32.0	-46.9	52.3	67.6	17.6
Mean	-8.7	-12.8	-32.2	-27.2	25.3	30.1	-17.9
p-Value	0.0002	<0.0001	0.0001	<0.001	<0.0001	0.0002	<0.0188
Combined	-8.7	-13.3	Gp B	-26.1	25.3	Gp B	Gp B
p-Value	0.0002	<0.0001	only	<.0001	<0.0001	only	only

Clinical trial- Liver Profile

THE EFFECT OF NIASPAN™ THERAPY ON AST (SGOT) LEVELS (U/L) (1500 mgs dosed once-a-day at night) (n = 28)

	Weeks Of Therapy With NIASPAN™				
Pt #	Baseline	2 Wks.	4 Wks.	8 Wks.	Reference Range
GROUP A					
1	28	29	25	24	0-50
2	24	25	24	26	0-50
3	17	18	22	21	0-50
4	14	16	15	17	0-50
5	22	NA	32	52	0-50
6	21	17	17	14	0-50
7	17	17	14	18	0-50
8	20	21	22	22	0-50
9	16	16	17	20	0-50
10	18	21	21	25	0-50
11	21	21	22	21	0-50

THE EFFECT OF NIASPAN™ THERAPY ON ALKALINE PHOSPHATASE LEVELS (U/L) (1500 mgs dosed once-a-day at night) (n = 28)

	Weeks Of Therapy With NIASPAN™				
Pt #	Baseline	2 Wks.	4 Wks.	8 Wks.	Reference Range
GROUP A					
1	52	56	57	55	20-140
2	103	100	89	102	20-140
3	54	45	53	51	20-140
4	70	68	71	91	20-140
5	77	NA	74	81	20-140
6	55	48	49	51	20-140
7	72	71	79	75	20-140
8	55	49	47	50	20-140
9	53	55	56	45	20-140
10	74	73	75	75	20-140
11	18	18	20	16	20-140

THE EFFECT OF NIASPAN™ THERAPY ON ALT (SGPT) LEVELS (U/L) (1500 mgs dosed once-a-day at night) (n = 28)

	Weeks Of Therapy With NIASPAN™				
Pt #	Baseline	2 Wks.	4 Wks.	8 Wks.	Reference Range
GROUP A					
1	32	28	39	30	0-55
2	24	25	23	26	0-55
3	18	23	30	30	0-55
4	7	13	14	14	0-55
5	14	NA	43	46	0-55
6	22	11	14	10	0-55
7	9	7	11	7	0-55
8	16	18	23	21	0-55
9	14	17	20	14	0-55
10	14	15	17	19	0-55
11	18	18	20	16	0-55

new technical teaching

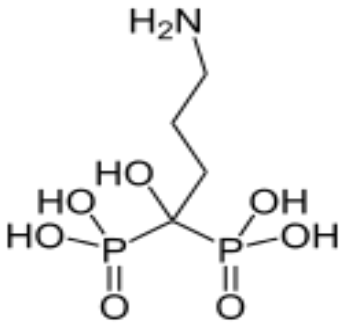
EP0643965
patent granted 22.04.2008

Il nuovo regime evita l'effetto avverso rappresentato dall'epatotossicità

T 1319/04

new dosing regimen

ALENDRONATO



OSTEOPOROSI

Somministrazione settimanale 70 mg
EP1175904
date of filling 17.07.1998

Somministrazione giornaliera
10 mg
IT1201087
patent granted 27.01.1989

Esophageal Irritation Potential Studies				
Group	**Active Agent mg/mL**	**Dosing Schedule**	**Sacrifice Time**	**Histo-pathology**
1 (n=4)	0	1X daily for 5 days	immediately after last dosing	Normal. Intact epithelium and absence of inflammatory cells in the submucosa.
2 (n=4)	Alendronate 0.20	1X daily for 5 days	immediately after last dosing	Deep ulceration of epithelial surface. Marked submucosal inflammation and vacuolation.
3 (n=5)	Alendronate 0.80	1X	24 hours after dosing	Intact epithelial surface with very slight submucosal inflammation and vacuolation.
4 (n=5)	Alendronate 0.80	1X	7 days after dosing	Intact epithelium with either minimal inflammation (2 of 5 animals) or no inflammation (3 of 5 animals) and no vacuolation.
5 (n=6)	Alendronate 0.80	1X weekly for a total of 4 doses	7 days after last dosing	Intact epithelium with no inflammation and no vacuolation.
6 (n=6)	Alendronate 0.40	2X weekly for 4 weeks	immediately after last dosing	Deep ulceration of epithelial surface. Marked submucosal inflammation and vacuolation.
7 (n=8)	Risedronate 0.20	1X daily for 5 days	immediately after last dosing	Deep ulceration of epithelial surface (4 of 8 animals). Marked submucosal inflammation and vacuolation.
8 (n=4)	Tiludronate 4.0	1X daily for 5 days	24 hours after last dosing	Slight submucosal inflammation and vacuolation (3 of 4 animals, including 1 of these animals with slight ulceration).

Profonda ulcerazione della superficie epiteliale, marcata infiammazione della sottomucosa

Epitelio intatto senza infiammazione

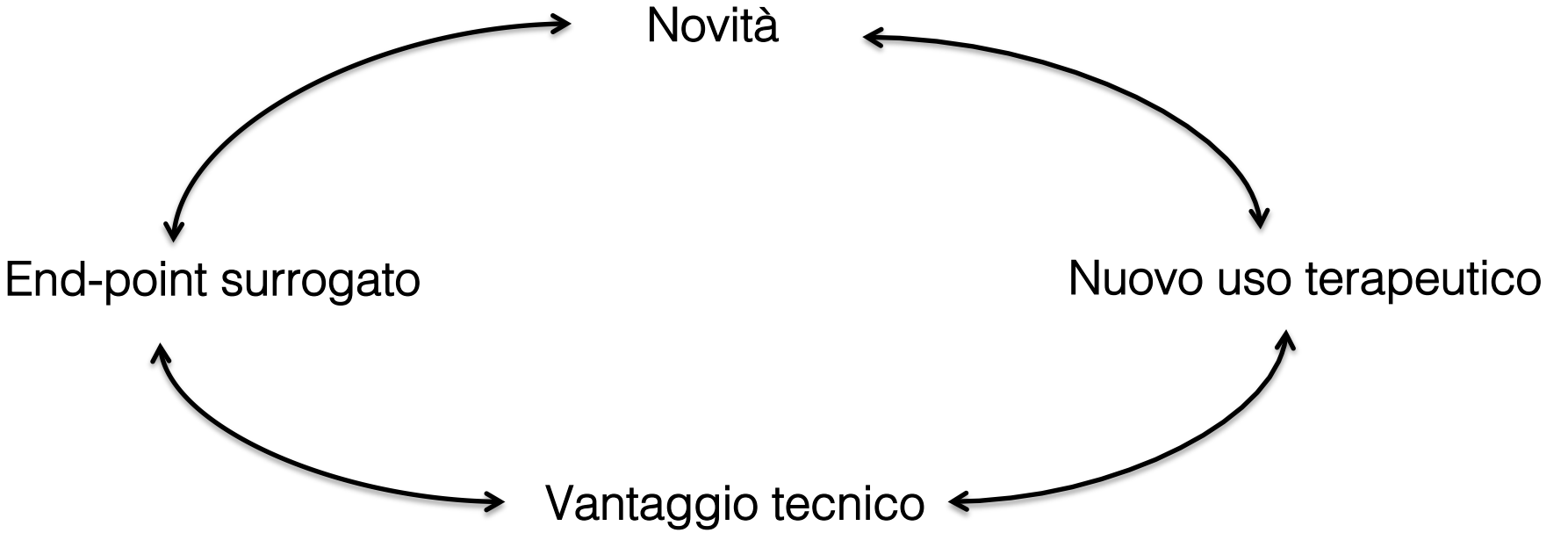
new technical teaching

Il nuovo regime:
- riduce gli effetti collaterali a livello esofageo
-migliora la compliance del paziente

EP1175904
patent **not** granted

T 1710/09

Minimum conditions to fulfill the requirements for patentability in the pharmaceutical sector



conclusioni

La conoscenza di questi concetti estrapolati dalla giurisprudenza dell'European Patent Office, unita alle altre innumerevoli possibilità di brevettazione esistenti nel settore farmaceutico, appare indispensabile ai ricercatori al fine di indirizzare i propri programmi di ricerca verso il conseguimento di risultati concretamente sfruttabili e valorizzabili al meglio mediante una valida protezione brevettuale.

grazie per l’attenzione