



No. 04-112812- -00006-0000

Fecha: 2007-09-28 16:19:43 Dep. 2020 NUECREACIONE acción
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Act. 329 CTOINFORMACION Folios: 14

Industria y Comercio
SUPERINTENDENCIA

FORMULARIO UNICO DE CORRECCIONES Y MODIFICACIONES

①

SOLICITUD DE

☐

Corrección de Error Material

☒

Modificación de una solicitud

②

SOLICITANTE

Nombre: KOREA MICROBIOLOGICAL LABORATORIES CO., LTD

Dirección: 1 RA-107, SHIHWA INDUSTRIAL COMPLEX
JUNGWANG-DONG, SHIHUNG CITY, KYONGGI-DO

Nacionalidad o Domicilio: REPUBLICA DE COREA

Lugar de Constitución:

Teléfono:

Fax:

E-Mail

IDENTIFICACION

C.C.

☐

NIT

☐

C.E.

☐

Otro

☐

Cual

Número

③

REPRESENTANTE
O APODERADO

Nombre: MAURICIO JARAMILLO CAMPUZANO

Dirección: CALLE 67 N 7-35 OFICINA 1204

Teléfono: 3192929

Fax: 310 6657

E-Mail: mjaramillo@gomezpinzon.com

IDENTIFICACION

C.C.

☒

NIT

☐

C.E.

☐

Otro

☐

Cual

Número

80.421.942

74.555

TP C.S.J.

④

Numero de expediente

04-112812

⑤

Descripción de la corrección o modificación solicitada

"CAMBIO DE NOMBRE DE KOREA MICROBIOLOGICAL LABORATORIES CO., LTD." A "KOMIPHARM INTERNATIONAL CO., LTD."

⑥

Comprobante de Pago No. 07-75939

Fecha SEPTIEMBRE 20 DE 2007

⑦

Anexos

☒

Comprobante de pago de la tasa.

☐

Poderes, si fuere el caso.

☐

Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

⑧

NOMBRE MAURICIO JARAMILLO CAMPUZANO

FIRMA

c.d. 80.421.942 TP 74.555

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

13

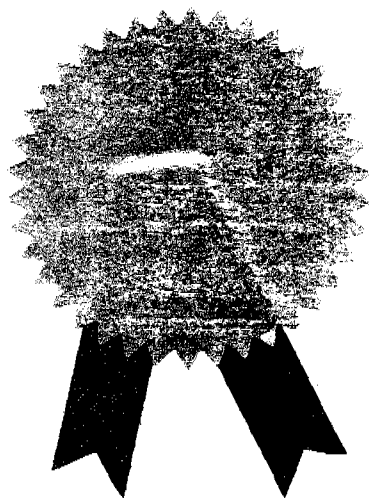
[제41호 서식]

대표전화 031) 414-9988

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Registered No. 2007 - 6383

NOTARIAL CERTIFICATE



THE NOTARY'S OFFICE, ANSANJEIL

2nd Floor, The Great Korea Law Bldg. 707-3

Gojan-dong, Danwon-gu, Ansan-city, Gyeonggi-do, Korea 425-806

NOTARIO SEXTO (F. DEL CIRCULO)
COMO NOTARIO SEXTO (F. DEL CIRCULO)
DE AGOSTA, HAGO CONSTAR QUE LA
FOTOCOPIA CONCIDE CON EL ORIGINAL
QUE HE TENIDO EN LA VISTA

25 JUL 2007

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433

Registered No.	005320	TRANSCRIPT OF REGISTER BOOK (Include Matters of Cancellation)
Registration No.	110111-0134372	
Trade Name : Korea Microbiological Laboratories Co., Ltd.(Erased)		Changed :
Komipharm International Co., Ltd.		Registered:
Head Office : 1Ra 107, Sihwa Industrial Complex.		Changed: Sep. 3, 2004
Jeongwang-dong, Siheung-si (Erased)		Registered: Sep. 3, 2004
1236-6, Jeongwang-dong, Siheung-si		Changed :
		Registered:
		Land readjustment
		completion: Aug. 11, 1993
		Registered: Mar. 28, 2006

Notification : Appearance in The Korea Economic Daily issued in Seoul	Changed :
	Registered:

Amount per One Stock : 500 Korean Won	Changed :Aug. 25, 2000
	Registered: Sep. 30, 2000

Total number of Stocks to be issued : 15,000,000 Stocks	Changed :Aug. 25, 2000
	Registered: Sep. 30, 2000

Total number of Stocks and the type & Number of each stock	Total amount of Capital	Data Changed :
Total number of Stocks to be issued:7,860,000(X) Common Stocks : 7,860,000 Stocks(X)	Amount:3,930,000,000 Won(X)	Data Registered:
Total number of Stocks to be issued:8,004,589(X) Common Stocks : 8,004,589 Stocks(X)	Amount:4,002,294,500 Won(X)	Changed : Oct. 19, 2001
Total number of Stocks to be issued:8,074,408(X) Common Stocks : 8,074,408 Stocks(X)	Amount:4,037,204,000 Won(X)	Registered: Oct. 19, 2001
Total number of Stocks to be issued:8,453,774 Common Stocks : 8,453,774 Stocks	Amount:4,226,887,000 Won	Changed : Mar. 18, 2005
		Registered: Mar. 23, 2005
		Changed : Dec. 31, 2005
		Registered: Jan. 3, 2006
		Changed : Mar. 24, 2006
		Registered: Apr. 4, 2006

Business Summary		
1. Manufacturing & Sale Business of Animal's Medicine (x)	< Erased-03.23.2004	Registered-03.23.2004>
2. Business related to Research & Investigation to the Prevention of epidemics (x)	< Erased-03.23.2004	Registered-03.23.2004>
3. Business related to Research & Investigation to disease treatment for domestic animal (x)	< Erased-03.23.2004	Registered-03.23.2004>
4. Manufacturing & Sale Business of Food additive (x)	< Erased-03.23.2004	Registered-03.23.2004>
5. Manufacturing & Sale Business of Soil conditioner & Special fertilizer (x)	< Erased-03.23.2004	Registered-03.23.2004>
6. Accessory business related to the above items.(x)	< Erased-03.23.2004	Registered-03.23.2004>
7. Manufacturing & Sale Business of the general germicidal & disinfection agent (x)	< Changed-03.31.1993	Registered-04.09.1993>
8. Manufacturing & Sale Business of the deodorizer (x)	< Changed-03.31.1993	Registered-04.09.1993>
9. Clinical pathology inspection, test analysis & Agent service (x)	< Erased-03.23.2004	Registered-03.23.2004>
10. Manufacturing & Sale Business of the Biologic, etc. (x)	< Changed-09.15.2000	Registered-09.16.2000>
	< Erased-03.23.2004	Registered-03.23.2004>
Can confirm bar-code of document lower column by scanner, or forgery variation availability because input issuance confirmation No. issuance confirmation menu of Internet registry.		
Confirmation through issuance confirmation No. is available limiting in 5th from date of issue to 3 months.		

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Registered No.	005320		
12. Manufacturing & Sale Business of the Environmental Microbe(Liquid waste treatment, disposal of garbage, purification of the water) (x)	< Changed-09.15.2000 < Erased-03.23.2004	Registered-09.16.2000> Registered-03.23.2004>	
13. Manufacturing & Sale Business of the Bio-fertilizer(Include Soil microbic agent) (x)	Changed-09.15.2000 < Erased-03.23.2004	Registered-09.16.2000> Registered-03.23.2004>	
14. Manufacturing & Sale Business of the diagnosis agent & medicine raw materials (x)	< Changed-09.15.2000 < Erased-03.23.2004	Registered-09.16.2000> Registered-03.23.2004>	
15. Lease business for Real estate & Machinery installation (x)	< Changed-09.15.2000 < Erased-03.23.2004	Registered-09.22.2000> Registered-03.23.2004>	
1. Manufacturing & Sale Business of Animal Medicine (x)			
2. R & D and Production Mfg. vaccination against every and all sorts of epidemic (x)			
3. Research for virus, germ, round worm, etc. Industrial microbe (x)			
4. Manufacturing & Sale Business of Food additive (x)			
5. Clinical pathology inspection, test analysis & Agent service (x)			
6. Lease business for Real estate & Machinery installation (x)			
7. Manufacturing & Sale Business of the Biologic, etc. (x)			
8. Manufacturing & Sale Business of Bio-fertilizer (Soil microbe agent) (x)			
9. Itemize & Sale Business of medicine, raw material medicine, manufacturing other than medicine (x)			
10. Itemize & Sale Business of health aid foodstuff manufacturing (x)			
11. Accessory Business related to each of the above items(x)	< Changed-03.18.2004	Registered-03.23.2004>	
1. Manufacturing & Sale Business of Animal Medicine			
2. R & D and Production Mfg. vaccination against every and all sorts of epidemic			
3. Research for virus, germ, round worm, etc. Industrial microbe			
4. Manufacturing & Sale Business of Food additive			
5. Clinical pathology inspection, test analysis & Agent service			
6. Lease business for Real estate & Machinery installation			
7. Manufacturing & Sale Business of the Biologic, etc.			
8. Manufacturing & Sale Business of Bio-fertilizer (Soil microbe agent)			
9. Itemize & Sale Business of medicine, raw material medicine, manufacturing other than medicine			
10. Itemize & Sale Business of health aid foodstuff manufacturing			
11. Manufacturing & Sale Business of the aid livestock feed.			
12. Trade Business in domestic and overseas and agent business.			
13. e-transactions and Internet related business.			
14. Accessory Business related to each of the above items.	< Addition-09.03.2004	Registered-09.03.2004>	

ON ALL NOTARIAL ACTS TO BE DELIVERED BY THE NOTARY PUBLIC, IT MUST BE CONSIDERED THAT THE ORIGINAL DOCUMENTS ARE TO BE KEPT IN THE OFFICE OF THE NOTARY PUBLIC FOR A PERIOD OF FIVE YEARS.

25 SET 2007

MATTERS RELATED TO EXECUTIVE

Director Yang, Yong Jin 530801-1011014

Inaugurated on March 21, 2001

Registered : March 23, 2001

Reappointed on March 21, 2004

Registered : March 23, 2001

Reappointed on March 21, 2004

Registered : March 23, 2004(Revised date of Register)

Reappointed on March 23, 2007

Registered : March 26, 2007

Issued No. -Omitted-

Date issued : Aug. 16, 2007

Issuance Confirmation No. 3205-ANLI-MHUK

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The Supreme Court

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Registered No.	005320	
Director Kim, Ju Baik 431225-1010614 (Erased)	Inaugurated on March 21, 2001 Resigned on May 31, 2003	Registered : March 23, 2001 Registered : June 3, 2003
Director Moon, Seong Cheol 591113-1110418	Inaugurated on March 21, 2001 Reappointed on March 21, 2004 Reappointed on March 23, 2007	Registered : March 23, 2001 Registered : March 23, 2004 Registered : March 26, 2007
Representative Director Yang, Yong Jin 530801-1011	014 254-4, Gumi-dong, Boondang-ku, Sungnam-city Inaugurated on March 21, 2001 Reappointed on March 21, 2004 Reappointed on March 23, 2007	Registered : March 23, 2001 Registered : March 23, 2004 Registered : March 26, 2007
Auditor Lee, Sang Bong 540924-1052225 (Erased)	Inaugurated on March 21, 2001 Resigned on March 21, 2004	Registered : March 23, 2001 Registered : March 23, 2004
Director Lem, Jai Kook 580915-1450712	Inaugurated on March 22, 2002 Reappointed on March 22, 2005	Registered : March 28, 2002 Registered : March 23, 2005
Auditor Hwang, Jung Yean 510425-1063113 (Erased)	Inaugurated on March 21, 2004 Resigned on March 24, 2006	Registered : March 23, 2004 Registered : March 28, 2006
Director Lee, Sang Bong 540924-1052225 (Erased)	Inaugurated on March 21, 2004 Resigned on March 31, 2006	Registered : March 23, 2004 Registered : April 4, 2006
Auditor Hwang, Jung Yean 510425-1063113	Inaugurated on March 24, 2006	Registered : March 28, 2006
Director Yu, Cheong Ki 460606-1024821	Inaugurated on March 23, 2007	Registered : March 26, 2007
Representative Director Moon, Seong Cheol 591113- 1110418	311-1602, Ansangojan 3cha pureujio, 728, Gogan-dong, Danwon-gu, Ansan-si Inaugurated on March 23, 2007	Registered : March 26, 2007

THE OTHER MATTERS	
2. Changed Registration No. 110111-0134372	Registered : Feb. 26, 1992
1. Proxy on owner's amendment, Trade name Certificate of Stock Depositing Bank (Erased) 33, Yeouido-dong, Yeongdungpo-ku, Seoul (Erased) Established on Apr. 7, 2000	Registered : Apr. 18, 2000
Certificate of Stock Depositing Bank (Erased) 34-6, Yeouido-dong, Yeongdungpo-ku, Seoul (Erased) Changed on Sep. 11, 2002	Registered : Sep. 2, 2002
Certificate of Stock Depositing Bank (Erased)	

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Registered No. 005320

34-6, Yeouido-dong, Yeongdungpo-ku, Seoul
Changed on Jan. 29, 2005
Registered : Feb. 3, 2005

MATTERS RELATED TO THE BRANCH OFFICE

256-1, Dukok-ri, Shinam-myun, Yesan-kun, Chungnam (Yesan Branch)
Established on Nov. 18, 1994
Zuidersluisweg 2, 8243 RC Lelystad, The Netherlands (Netherlands branch) (Erased)
Established on Jan. 13, 2005
Closed on Dec. 14, 2005
Registered : Nov. 19, 1994
Registered : Jan. 26, 2005
Registered : Dec. 15, 2005

CONVERTIBLE BOND

1. The 1st Convertible bond (Erased)
The Amount of Convertible bond : 1,200,000,000 Won (Erased)
The Amount of each Convertible bond : 100,000,000 Won, 10,000,000 Won (Erased)
The Amount paid up for Convertible bond : 1,200,000,000 Won (Erased)
This Bond can be converted into stocks (Erased)
The Convertible condition : 17,000 Won per face value (Erased)
The Contents of stocks to be issued by convertible bond : 17,500 Won per value of common stock. (Erased)
Period of request for conversion shall be full 3 years from the date of debenture issued (Erased)
< Registered : Dec. 28, 2004 >

1. The 1st Convertible bond (Erased)
The Amount of Convertible bond : 1,200,000,000 Won (Erased)
The Amount of each Convertible bond : 100,000,000 Won, 10,000,000 Won (Erased)
The Amount paid up for Convertible bond : 1,200,000,000 Won (Erased)
This Bond can be converted into stocks (Erased)
The Convertible condition : 17,000 Won per face value (Erased)
The Contents of stocks to be issued by convertible bond : 17,500 Won per value of common stock. (Erased)
Period of request for conversion : Shall be fixed from the passage of 1 year after the issuance of bond prior to the due date of One(1) month. (Erased)
< Erroneous requesting date : Registered : Dec. 31, 2004 >

1. The 1st Convertible bond (Erased)
The Amount of Convertible bond : 1,200,000,000 Won (Erased)
The Amount of each Convertible bond : 100,000,000 Won, 10,000,000 Won (Erased)
The Amount paid up for Convertible bond : 1,200,000,000 Won (Erased)
This Bond can be converted into stocks (Erased)
The Convertible condition : 17,187 Won per face value (Erased)
The Contents of stocks to be issued by convertible bond : 17,500 Won per value of common stock. (Erased)
Period of request for conversion : Shall be fixed from the passage of 1 year after the issuance of bond prior to the due date of One(1) month. (Erased)
< Condition face amount alteration of conversion : Dec. 29, 2005 Registered : Jan. 3, 2006 >
< All stocks conversion : Dec. 31, 2005 Registered : Jan. 3, 2006 >

25 SEP 2007
COMPROBADO EN EL CIRCULO
DE BOGOTA HASTA CONSTAR QUE LA
COPIA CONCUERDE CON EL ORIGINAL
QUE SE TIENE A LA VISTA

STOCK OPTION

1. Ground of present : The Staff who contributed or Will be contribute to the establishment of company, management, overseas business and technological innovation. (Erased)

Issuance Confirmation No. 3205-ANLI-MHUK

Issued No. -Omitted-

Date issued : Aug. 16, 2007

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The Supreme Court

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Registered No.	005320
2. Objective person to be presented : Lee, Sang Bong (Erased) 3. Number of stocks to be presented : Common stock 130,000 stocks (Erased) 4. Method of present : Exchange by issuing new stocks. (Erased) 5. Price of exercise : Observation of the Regulations stipulated in the Securities and Exchange Act. Enforcement Law Article 84-6. (Erased) 6. Period of holding event : March 18, 2008 through March 17, 2015. (Erased) 7. Price adjustment : After the date of present the right of selection for stock acquiring by purchase, in case of free issue of new stock or onerous increase capital, stock dividend, division stock, capital input of the capital reserve or face value share, the matters related to exercise value & quantity adjustment shall be of resolution of the Board of Director's Meeting. (Erased) 8. The others : Those items not contained in the above content shall be of every and all regulations, the Company Article of Association, Agreement, etc. related to the right of exercise for share acquiring by purchase. (Erased) < Change on < Closed on Mar. 31, 2006 Registered : Mar. 23, 2005 > Registered : Apr. 4, 2006 >	

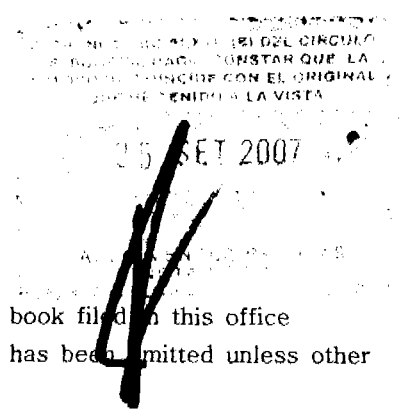
Date of Company founded :	Sep. 21, 1972
---------------------------	---------------

Reason for opening of Registration from & Date
Transcribed from previous register pursuant to the Commercial Register Treatment Regulation, Bylaw, Article 2-1.
Registered : Apr. 29, 2002

-- Blank below --

Receipt Service charge : 1,200 Won

Issued by : Sihung Registry Asan Branch,
Suwon District Court



This is to certify that the above statement is a transcript of the original register book filed in this office {The matters of registration invalid and Manager(Proxy), Branch (Division Office) has been omitted unless other wise application}

August 16, 2007

/s/Official Seal Affixed
Kang, Han su
Registrar
Asan Registration Division

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등기번호	005320
등록번호	110111-0134372

등기부 등본 (말소사항 포함)

상 호	株式會社 韓國微生物研究所	변경 등기
	주식회사 코미팜	2004.09.03 변경 2004.09.03 등기
본 점	시흥시 정왕동 사회공단 1라 107	변경 등기
	시흥시 정왕동 1236-6	1993.08.11 구획 정리 완료 2006.03.28 등기

광고방법	서울시내에서 발행하는 일간 한국경제신문에 게재한다.	변경 등기
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1주의 금액	금 500 원	2000.08.25 변경 2000.09.30 등기
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발행할 주식의 총수	15,000,000 주	2000.08.25 변경 2000.09.30 등기
------------	--------------	--------------------------------

발행주식의 총수와 그 종류 및 각각의 수	자본의 총액	변경 연월일 등기 연월일
발행주식의 총수 7,860,000 주		2001.10.19 변경
보통주식 7,860,000 주	금 3,930,000,000 원	2001.10.19 등기
발행주식의 총수 8,004,589 주		2005.03.18 변경
보통주식 8,004,589 주	금 4,002,294,500 원	2005.03.23 등기
발행주식의 총수 8,074,408 주		2005.12.31 변경
보통주식 8,074,408 주	금 4,037,204,000 원	2006.01.03 등기
발행주식의 총수 8,453,774 주		2006.03.24 변경
보통주식 8,453,774 주	금 4,226,887,000 원	2006.04.04 등기

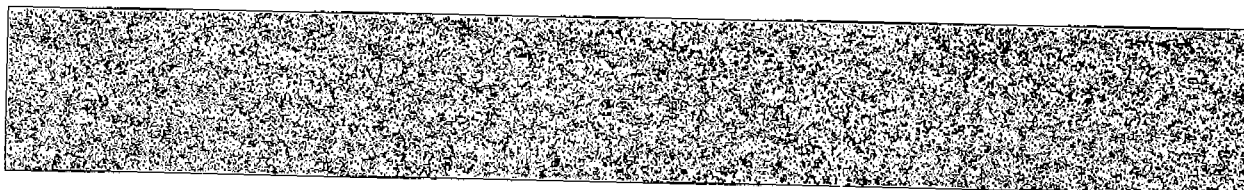
목	적
1. 동물약품제조 및 판매업	<2004.03.23 삭제 2004.03.23 등기>
2. 방역에 관한 연구조사에 관한 사업	<2004.03.23 삭제 2004.03.23 등기>
3. 가축질병치료에 관한 연구 조사에 관한사업	<2004.03.23 삭제 2004.03.23 등기>
4. 식품첨가물제조 및 판매업	<2004.03.23 삭제 2004.03.23 등기>
5. 특수비료 및 토양개량제 제조 및 판매업	<2004.03.23 삭제 2004.03.23 등기>
6. 각종에 관련된 부대사업	<2004.03.23 삭제 2004.03.23 등기>
7. 일반살균소독제 제조 및 판매업	<1993.03.31 변경 1993.04.09 등기>
8. 방취제 제조 및 판매업	<2004.03.23 삭제 2004.03.23 등기>
	<1993.03.31 변경 1993.04.09 등기>
9. 임상병리 검사, 시험, 분석 및 대행 서비스업	<2004.03.23 삭제 2004.03.23 등기>
	<1998.08.06 변경 1998.08.10 등기>
10. 생물학적 재재등의 제조 및 판매업	<2004.03.23 삭제 2004.03.23 등기>
	<2000.09.15 변경 2000.09.16 등기>

문서 하단의 바코드를 스캐너로 확인하거나, 인터넷등기소(<http://www.iros.go.kr>)의 발급확인 메뉴에서 발급확인번호를 입력하여 위·변조 여부를 확인할 수 있습니다.
발급확인번호를 통한 확인은 발행일부터 3개월까지 5회에 한하여 가능합니다.

발급확인번호 3206-ANLI-MHUC

00000210301263158000710105255301B9DABFECC1F819690922 10 발행일:2007/08/16

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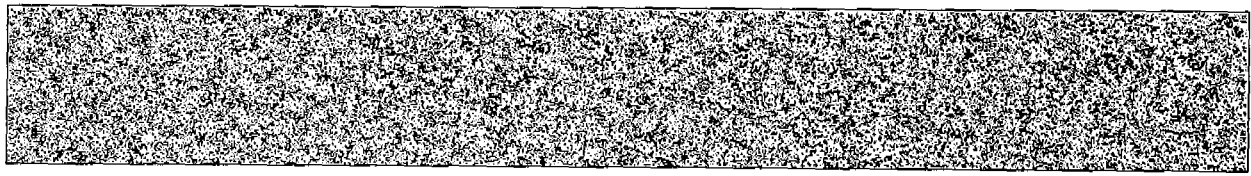
등기번호	005320			
		<2004.03.23	삭제	2004.03.23 등기>
12. 환경미생물(폐수처리, 오물처리, 수질정화등)의제조 및 판매업				
		<2000.09.15	변경	2000.09.16 등기>
		<2004.03.23	삭제	2004.03.23 등기>
13. 바이오비료(토양미생물제제포함) 제조 및 판매업		<2000.09.15	변경	2000.09.16 등기>
		<2004.03.23	삭제	2004.03.23 등기>
14. 진단사약 및 의약품원료 제조 및 판매업		<2000.09.15	변경	2000.09.16 등기>
		<2004.03.23	삭제	2004.03.23 등기>
15. 부동산 및 기계설비 임대업		<2000.09.15	변경	2000.09.22 등기>
		<2004.03.23	삭제	2004.03.23 등기>
1. 동물용 의약품등 제조 및 판매업				
2. 각종 전염병 질병예방을 위한 백신의 연구개발 및 생산제조				
3. 바이러스, 세균 및 원충등 산업미생물에 관한 연구				
4. 식품첨가물제조 및 판매업				
5. 임상병리검사, 시험, 분석 및 대행서비스업				
6. 부동산 및 기계설비 임대업				
7. 생물학적 제제등의 제조 및 판매업				
8. 바이오비료(토양미생물제제 포함)제조 및 판매업				
9. 의약품, 원료의약품, 의약외품제조, 소분 및 판매업				
10. 건강보조식품 제조, 소분 및 판매업				
11. 각항에 관련된 부대사업		<2004.03.18	변경	2004.03.23 등기>
1. 동물용 의약품등 제조 및 판매업				
2. 각종 전염병 질병예방을 위한 백신의 연구개발 및 생산제조				
3. 바이러스, 세균 및 원충등 산업미생물에 관한 연구				
4. 식품첨가물제조 및 판매업				
5. 임상병리검사, 시험, 분석 및 대행서비스업				
6. 부동산 및 기계설비 임대업				
7. 생물학적 제제등의 제조 및 판매업				
8. 바이오비료(토양미생물제제 포함)제조 및 판매업				
9. 의약품, 원료의약품, 의약외품제조, 소분 및 판매업				
10. 건강보조식품 제조, 소분 및 판매업				
11. 보조사료 제조 및 판매업				
12. 국내외 무역업 및 무역대리업				
13. 전자상거래 및 인터넷 관련사업				
14. 전 각항에 부대되는 사업		<2004.09.03	추가	2004.09.03 등기>

NOTARIO (CENTRO) DEL CIRCULO
DE POLICIA HAGO CONSTAR QUE LA
FOTOCOPIA CONCIDE CON EL ORIGINAL
QUE SE ENCONTRA A LA VISTA
25 SET 2007

임원에 관한 사항

이사 양용진 530801-1011014

2001 년 03 월 21 일	취임	2001 년 03 월 23 일	등기
2004 년 03 월 21 일	중임	2001 년 03 월 23 일	등기
2004 년 03 월 21 일	중임	2004 년 03 월 23 일	등기(등기일자경정)
2007 년 03 월 23 일	중임	2007 년 03 월 26 일	등기



70 70

등기번호	005320
~~이사 김주백 431225-1010614~~	
2001 년 03 월 21 일 취임	2001 년 03 월 23 일 등기
2003 년 05 월 31 일 사임	2003 년 06 월 03 일 등기
~~이사 문성철 591113-1110418~~	
2001 년 03 월 21 일 취임	2001 년 03 월 23 일 등기
2004 년 03 월 21 일 중임	2004 년 03 월 23 일 등기
2007 년 03 월 23 일 중임	2007 년 03 월 26 일 등기
~~대표이사 양용진 530801-1011014 성남시 분당구 구미동 254-4~~	
2001 년 03 월 21 일 취임	2001 년 03 월 23 일 등기
2004 년 03 월 21 일 중임	2004 년 03 월 23 일 등기
2007 년 03 월 23 일 중임	2007 년 03 월 26 일 등기
~~감사 이상봉 540924-1052225~~	
2001 년 03 월 21 일 취임	2001 년 03 월 23 일 등기
2004 년 03 월 21 일 퇴임	2004 년 03 월 23 일 등기
~~이사 임재국 580915-1450712~~	
2002 년 03 월 22 일 취임	2002 년 03 월 28 일 등기
2005 년 03 월 22 일 중임	2005 년 03 월 23 일 등기
~~감사 황정연 510425-1063113~~	
2004 년 03 월 21 일 취임	2004 년 03 월 23 일 등기
2006 년 03 월 24 일 사임	2006 년 03 월 28 일 등기
~~이사 이상봉 540924-1052225~~	
2004 년 03 월 21 일 취임	2004 년 03 월 23 일 등기
2006 년 03 월 31 일 사임	2006 년 04 월 04 일 등기
~~감사 황정연 510425-1063113~~	
2006 년 03 월 24 일 취임	2006 년 03 월 28 일 등기
~~이사 유정기 460606-1024821~~	
2007 년 03 월 23 일 취임	2007 년 03 월 26 일 등기
~~대표이사 문성철 591113-1110418 안산시 단원구 고잔동 728 안산고잔3차푸르지오 311동 1602호~~	
2007 년 03 월 23 일 취임	2007 년 03 월 26 일 등기

기 타 사 항	
2. 등록번호 개정 110111-0134372	1992 년 02 월 26 일 등기
1. 명의개서대리인의 상호 및 본점소재지 증권예탁원 서울 영등포구 여의도동 33 2000 년 04 월 07 일 설치	2000 년 04 월 18 일 등기
증권예탁원 서울 영등포구 여의도동 34-6 2002 년 09 월 11 일 변경	2002 년 10 월 02 일 등기
증권예탁결제원	

COMO NOTARIO SEXTO (E) DEL CIRCULO
ROGGA MAGO CONSTAR QUE LA
FOTOCOPIA CONCORDA CON EL ORIGINAL
QUE SE TIENE A LA VISTA

25 OCT 2007



지

등기번호 005320

서울 영등포구 여의도동 34-6
2005 년 01 월 29 일 변경 2005 년 02 월 03 일 등기

지점에 관한 사항
충남 예산군 신암면 두곡리 256-1(예산지점)
1994 년 11 월 18 일 설치 1994 년 11 월 19 일 등기
네덜란드 펠리스타드 알씨 8243 주아다스루이스배그 2(네덜란드지점)
2005 년 01 월 13 일 설치 2005 년 01 월 26 일 등기
2005 년 12 월 14 일 폐지 2005 년 12 월 15 일 등기

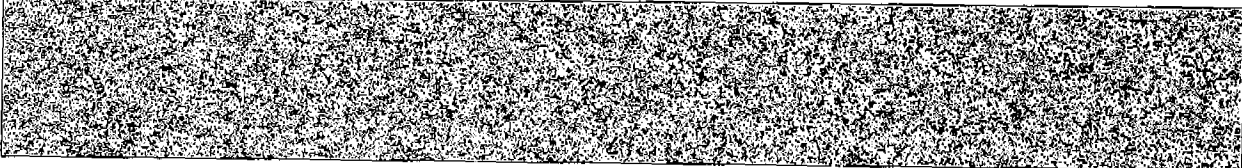
전 환 사 채

1. 제1회 전환사채
 전환사채의 총액 금 1,200,000,000원
 각 전환사채의 금액 금100,000,000원, 금10,000,000원
 각 전환사채의 납입금액 금 1,200,000,000원
 본 사채는 이를 주식으로 전환할 수 있다.
 전환의 조건 액면 금17,500원에 대하여 1주의 비율
 전환으로 발행할 주식의 내용 1주의 금액 금17,500원 보통주식
 전환을 청구할 수 있는 기간 사채발행일로부터 만3년간
 < 2004 년 12 월 28 일 등기 >

1. 제1회 전환사채
 전환사채의 총액 금 1,200,000,000원
 각 전환사채의 금액 금100,000,000원, 금10,000,000원
 각 전환사채의 납입금액 금 1,200,000,000원
 본 사채는 이를 주식으로 전환할 수 있다.
 전환의 조건 액면 금17,500원에 대하여 1주의 비율
 전환으로 발행할 주식의 내용 1주의 금액 금17,500원 보통주식
 전환을 청구할 수 있는 기간 사채발행일로부터 1년이 경과된 날로부터 만기일1개월전까지
 < 년 월 일 신청작오 2004 년 12 월 31 일 등기 >

1. 제1회 전환사채
 전환사채의 총액 금 1,200,000,000원
 각 전환사채의 금액 금100,000,000원, 금10,000,000원
 각 전환사채의 납입금액 금 1,200,000,000원
 본 사채는 이를 주식으로 전환할 수 있다.
 전환의 조건 액면 금17,187원에 대하여 1주의 비율
 전환으로 발행할 주식의 내용 1주의 금액 금17,500원 보통주식
 전환을 청구할 수 있는 기간 사채발행일로부터 1년이 경과된 날로부터 만기일1개월전까지
 < 2005 년 12 월 29 일 전환의조건액면금변경 2006 년 01 월 03 일 등기 >
 < 2005 년 12 월 31 일 전부주식전환 2006 년 01 월 03 일 등기 >

주식매수선택권
1. 부여근거 : 회사의 설립, 경영, 해외영업과 기술혁신등에 기여하거나 기여할 수



대명원

11

1007 13

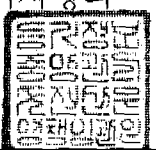
등기번호	00000210301263158000710105255301B9DABFECC1F819690922 10
1. ~~상호명~~	
2. ~~부여대상자~~ 이 상봉	
3. ~~부여주식수~~ 보통주 130,000주	
4. ~~부여방법~~ 신주를 발행하여 교부	
5. ~~행사가격~~ 증권거래법 시행령 제84조의6 제4항의 규정을 준용	
6. ~~행사기간~~ 2008년 3월 18일부터 2015년 3월 17일까지	
7. ~~가격조정~~ 주식매수선택권 부여일 이후 유,무선증자, 주식배당, 주식분할, 준비금의 자본전입 또는 액면분할등을 하는 경우의 행사가격 및 수량등의 조정 에 관한 사항은 이사회회의 결의에 따른다.	
8. ~~기타~~ : 상기내용에 포함되지않은 사항은 주식매수선택과 관련된 제반법규,당사정관 계약서등에 정하는 바에 따른다.	
< 년 월 일 변경 2005 년 03 월 23 일 등기 >	
< 2006 년 03 월 31 일 폐지 2006 년 04 월 04 일 등기 >	

회사성립연월일	1972 년 09 월 21 일
---------	------------------

등기용지의 개설 사유 및 연월일
상업등기처리규칙 부칙 제2조 1항의 규정에 의하여 구등기로부터 이기
2002 년 04 월 29 일 등기

수수료 1,200원 영수함 --- 이 하 여 백 ---
관할등기소 : 수원지방법원 안산지원 시흥등기소 / 발행등기소 : 수원지방법원 안산지원 시흥등기소

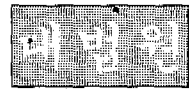
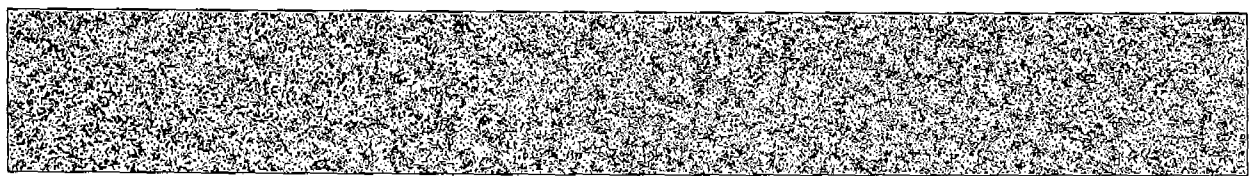
등기부 등본(말소사항 포함)입니다. [다만, 신청이 없는 경우에는 효력이 없는 등기사항과 지배인(대리인), 지점(분사무소)의 등기사항을 생략하였습니다.]
서기 2007년 08월 16일
법원행정처 등기정보중앙관리소 전산운영책임관 강한수



* 실선으로 그어진 부분은 말소(변경,경정)된 등기사항입니다. * 등기부는 컬러 또는 흑백으로 출력 가능합니다.
문서 하단의 바코드를 스캐너로 확인하거나, 인터넷등기소(<http://www.iros.go.kr>)의 발급확인 메뉴에서
발급확인번호를 입력하여 위·변조 여부를 확인할 수 있습니다.
발급확인번호를 통한 확인은 발행일부터 3개월까지 5회에 한하여 가능합니다.

발급확인번호 3206-ANLI-MHUC
00000210301263158000710105255301B9DABFECC1F819690922 10 발행일:2007/08/16 - 5/5 -

26
24



[제45호 서식]

위 번역문은 원문과 상위 없음을
서약합니다.

I swear that the attached translation
is true to the original.

2007. 8. 17.

Aug. 17, 2007

서약인

이 상언

Signature

Lee, Sang Un

등부 2007년 제 6383 호

Registered No. 2007 - 6383

인 증

Notarial Certificate

위 이 상 언 은(는)
본직의 면전에서 위 번역문이
원문과 상위 없음을 확인하고
서명 하였다.

Lee Sang Un personally
appeared before me, confirmed that the
attached translation is true to the original
and subscribed(seal) his(her) name.

2007년 8월 17일 이 사무소에서
위 인증한다.

This is hereby attested on this 17th
day of Aug., 2007 at this office.

안산제일 공증인 합동사무소

THE NOTARY'S OFFICE, ANSANJEIL

경기도 안산시 단원구 고잔동 707-3
대한법조 2층

2nd Floor, The Great Korea Law Bldg. 707-3

Gojan-dong, Danwon-gu, Ansan-city, Gyeonggi-do, Korea

4215-8006

NOTARIO PUBLICO (E) DEL CIRCULO
NOTARIAL HA DE CONSTAR QUE LA
FOTOCOPIA COINCIDE CON EL ORIGINAL
QUE SE TIENIO A LA VISTA

25 SEP 2007

공 증 인

박 상 진

Notary Public

Park Sang Jin

본 사무소는 2003년 9월 29일 법률
제723호에 의거, 법무부장관으로부터
공증인으로 임명받아 설치를 인가
받은 공증인합동사무소이다.

This office has been authorized by
the Minister of justice, the Republic
of Korea, to act as Notary Public
since Sept. 29, 2003 under Law No.
723.

APOSTILLE
(Convention de La Haye du 5 octobre 1961)

1. Country : Republic of Korea

This public document

2. has been signed by PARK SANG JIN

3. acting in the capacity of

4. bears the seal/stamp of AHNSAN LAW NOTARY OFFICE

Certified

5. at Seoul

6. 17/08/2007

7. by The Ministry of Foreign Affairs and Trade

8. No. 07-01-0003697

9. Seal/ stamp

10. Signature



W.S. Cho

Cho Woo-seok

RECEIVED
MINISTRY OF FOREIGN AFFAIRS AND TRADE
17/08/2007
13

301 KOREA

78/15

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 900176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 04-112812- -00006-0000

Fecha: 2007-09-28 16:19:43 Dep: 2020 NUECREACIONE
Tra: 11 PA... TELIYI Eva: 379 PASLNACIONALI
Act: 329 C... INFORMACION Folios: 14

RECIBO OFICIAL DE CAJA : 07 - 75,939
FECHA : SEPTIEMBRE 20 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
GOMEZ PINZON ASEMARCA	CONSIGNACION	BANCO POPULAR	050-00110-6	59810311	19/09/2007	20,682,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-06	REGISTRO DE CESION, CAMBIO NOM	
		13 NOMBRES Y ENSENAS COMERCIALES, MAR	243,000.00
		TOTAL :	\$ 243,000.00

SON: DOSCIENTOS CUARENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

DIVISION DE NUEVAS CREACIONES

7/6
24

RADICACIÓN EXPEDIENTE No 04-112812

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **562** DE

FECHA **31 DE MARZO DE 2006** EL TERMINO HABIL EÑALADO POR LA LEY

EXPIRA EL **05 DE JULIO DEL 2006**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO__ _X_ __

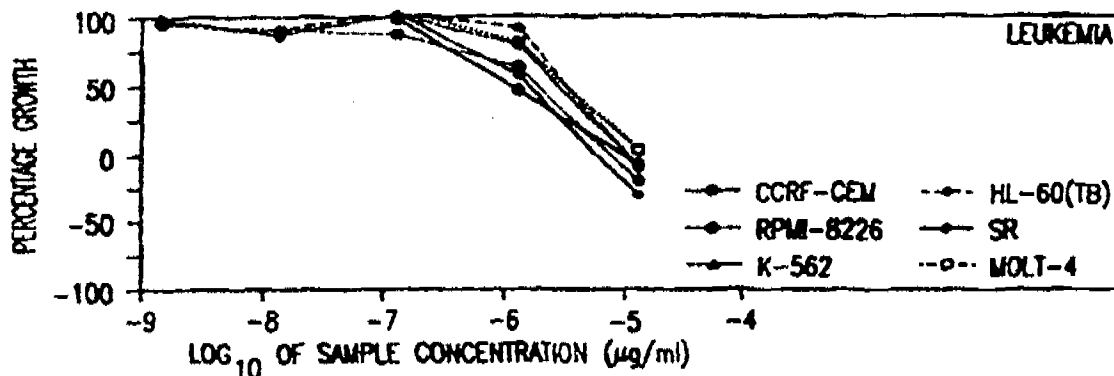


22
A2

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6: A01N 59/22		A1	(11) International Publication Number: WO 99/18798
			(43) International Publication Date: 22 April 1999 (22.04.99)
(21) International Application Number: PCT/US98/21782		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 15 October 1998 (15.10.98)			
(30) Priority Data: 60/062,375 15 October 1997 (15.10.97) US			
(71) Applicant: POLARX BIOPHARMACEUTICALS, INC. [US/US]; 48th floor, 787 Seventh Avenue, New York, NY 10019 (US).			
(72) Inventors: ELLISON, Ralph, M.; 218 Mediterranean Road, Palm Beach, FL 33480 (US). MERMELSTEIN, Fred, H.; 8 Skyview Terrace, Clifton, NJ 07013 (US).		Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	
(74) Agents: POISSANT, Brian, M. et al.; Pennie & Edmonds LLP, 1155 Avenue of the Americas, New York, NY 10036 (US).			

(54) Title: COMPOSITIONS AND METHODS FOR THE TREATMENT OF PRIMARY AND METASTATIC NEOPLASTIC DISEASES USING ARSENIC COMPOUNDS



(57) Abstract

The invention relates to the use of arsenic compounds to treat a variety of neoplastic diseases (see the dose response curves in the Figure). Further, the arsenic compounds may be used to treat metastatic neoplastic diseases.

anti-cancer agents are needed to be added to the arsenal against cancer.

3. SUMMARY OF THE INVENTION

5 Notwithstanding the conflicting reports in the art concerning benefits and risks of the administration of arsenic to patients, applicants have discovered that arsenic compound has broad applicability in the treatment of various cancers, including solid tumors and blood disorders. For
10 example, the present invention encompasses the use of arsenic in the form of a salt, complex, organic compound or ionic solution to treat tumors of epithelial tissue, connective tissue, central nervous system, lymphoid tissue, hematopoietic cells and tumors associated with oncogenic
15 viruses.

 Further, the present invention encompasses the use of arsenic compounds to treat mammals suffering from primary and metastatic neoplastic disease as well as infectious diseases related thereto.

20 In addition, this invention also encompasses the use of arsenic compounds to treat primary and metastatic breast, lung, bladder and prostate cancers in humans.

 This invention also encompasses the treatment of hematopoietic disorders in mammals by the administration of
25 one or more arsenic compounds to said mammal. The hematopoietic disorders to be treated include but are not limited to polycythemia vera, Hodgkin's Disease, non-Hodgkin's Disease including Follicular Lymphoma, Diffuse Lymphoma, lymphoblastic lymphoma, small lymphocytic lymphoma,
30 acute lymphocytic leukemia, hairy cell leukemia, myeloid metaplasia, myeloid dysplastic syndrome, multiple myeloma and plasmacytoma.

 In accordance with the present invention, arsenic compounds can be used alone or in combination with other
35 known therapeutic agents (including chemotherapeutics, radioprotectants and radiotherapeutics) or techniques to either improve the quality of life of the patient, or to

treat the primary neoplastic disease. For example, the arsenic compounds can be used before, during or after the administration of one or more known antitumor agents including but not limited to mustard compounds, nitrogen mustard, chlorambucil, melphalan, cyclophosphamide, 6-mercaptapurine, 6-thioguanine, cytarabine, 5-fluorouracil, floxuridine, methotrexate, vincristine, vinblastine, taxol, etoposide, temiposide, dactinomycin, daunorubicin, doxorubicin, bleomycin, mitomycin, cisplatin, carboplatin, estramustine phosphate, hydroxyurea, BCNU, procarbazine, VM-26 (vumon), interferons and all-trans retinoic acid (ATRA), (See for example, the Physician Desk References 1997). In addition, the arsenic compounds can be used before, during or after irradiation treatment. For the treatment of HIV-infected individuals, the arsenic compounds can be used alone or in combination with AZT, ddI, ddA, ddC, d4T, 3TC and other known antiviral agents.

The invention described herein encompasses a method of treating primary and metastatic neoplastic diseases, a method of treating solid tumors, a method of treating leukemias, a method of treating cancers related to bcl-2 (oncogene), each of which comprises the administration of a therapeutically effective and non-lethal amount of one or more arsenic compounds to a mammal in need of such therapy. The invention, as mentioned above also encompasses the use of combination therapy to treat the aforementioned diseases.

In a particular embodiment, the arsenic compounds are used within a method to treat breast, lung, colon, ovarian, renal, non-small cell lung, central nervous system, bladder, prostate and head and neck cancer by administering an effective amount of one or more arsenic compounds alone or in combination with other antineoplastic agents or therapeutic techniques including radiotherapy and surgery.

Without being limited by any theory, the inventors believe that the arsenic compounds of the invention may have one or more mechanisms of action in connection with the methods described herein. For example, the arsenic compounds

lines tested after continuous exposure to 10^{-5} to 10^{-9} $\mu\text{g/ml}$ of arsenic trioxide for 6 days.

5. DETAILED DESCRIPTION OF THE INVENTION

5 Methods and compositions for the treatment of primary and metastatic neoplastic diseases are described herein. The invention is based, in part, on a dosage regimen for administration of compositions comprising arsenic. The invention is also based in part, on the potency of the
10 arsenic compounds of the invention against certain cancers.

This invention includes a method of treating primary solid tumors in a mammal which comprises administering to a mammal in need of such therapy a therapeutically effective and non-lethal amount of one or
15 more arsenic compound.

The invention also includes a method of treating metastatic tumors in a mammal which comprises administering to a mammal a therapeutically effective and non-lethal dose of one or more arsenic compound.

20 The invention includes a method for treating disorders of blood in mammal which comprises administering one or more arsenic compound in a therapeutically effective and non-lethal amount.

The arsenic compound of the invention may be
25 utilized in in a variety of known forms; for example, arsenic can be administered as a salt, an organic or inorganic complex, an organic chelate, an organic compound or an organic or inorganic solution. It is preferred that the form be chosen to reduce toxicity and improve efficacy. Further,
30 the form chosen may also depend on the type and location of the tumor in question. The inorganic salt forms of arsenic are preferred. For example, inorganic salts such as arsenic triiodide, arsenic(III)bromide, arsenic(III)chloride, arsenic pentoxide, arsenic trioxide, Fowler's solution (potassium
35 arsenite), sodium arsenite, and calcium arsenite may be used. Arsenic trioxide is most preferred. Both arsenous acids and arsenites as well as arsenic acids and arsenates may be used

within the present methods. Aqueous solutions containing arsenite ions are preferred. Further, arsenic sulfides may be used such as arsenous sulfide, arsenic sulfide, arsenic pentasulfide, tetraarsenic trisulfide and tetraarsenic pentasulfide. Without being limited by any theory, certain of these arsenic compounds may be prodrugs to an active species.

Generally, the skilled artisan will recognize that the form of arsenic to be used should be therapeutically effective without unreasonable toxicity. The toxicity is dependent upon the dose, the dosage form, the mode of administration and frequency of dosing. Generally, the skilled artisan can chose from the following known forms of arsenic: arsenic halides, arsenic oxides, arsenic acids, arsenic sulfides, and the like.

Arsenic can also be readily combined with carbon to form a wide variety of organic compounds. These include but are not limited to primary and secondary arsines, tertiary arsines, halo arsines, dihalo arsines, cyclic and polymeric substances containing arsenic; specific examples of organic arsenic compounds include but are not limited to 3-Nitro-4-hydroxyphenylarsonic acid, arsanilic acid, sodium hydrogen 4-aminophenylarsenate, melarsoprol, melarsonyl potassium, carbarsone, arsenamide arspenamine and sodium arsanilate.

As used herein, "arsenic compound" refers to a pharmaceutically acceptable form of arsenic including salts, solutions, complexes, chelates and organic and inorganic compounds incorporating arsenic. It should be recognized that the invention includes arsenic prodrugs or compounds that are converted in vivo to biologically active forms of arsenic. Such prodrugs may be used to reduce or avoid the well known potential for arsenic toxicity. The arsenic compounds of the present invention can be synthesized or commercially purchased. For example, the compounds can be prepared from well-known chemical techniques. (See for example, Kirk-Othmer, Encyclopedia of Chemical Technology 4 ed. volume 3 pps. 633-655 John Wiley & Sons).

In one embodiment, the arsenic compound of the invention is arsenic trioxide which is dissolved in an aqueous solution of sodium hydroxide, with the pH adjusted to a physiologically acceptable range, e.g. about pH 6-8.

Any suitable mode of administration may be used in accordance with the present invention including but not limited to parenteral administration such as intravenous, subcutaneous, intramuscular and intrathecal administration; oral, intranasal, rectal or vaginal administration may also be used; directly into the tumor; transdermal patches; implant devices (particularly for slow release); finally, topical administration may be used. The mode of administration will vary according to the type of arsenic compound being used and the disease to be treated.

The pharmaceutical compositions to be used may be in the form of sterile physiologically acceptable (aqueous or organic) solutions, colloidal suspensions, creams, ointments, pastes, capsules, caplets, tablets and cachets. The pharmaceutical compositions comprising arsenic compounds of the invention can be contained in sealed sterile glass containers and/or ampoules. Further, the active ingredient may be micro-encapsulated, encapsulated in a liposome, noisome or lipof foam alone or in conjunction with targeting antibodies. It should be recognized that delayed slow or sustained release forms of administration are also included.

The arsenic compounds of the present invention may be used against a variety of primary and metastatic neoplastic diseases including but not limited to primary and metastatic tumors of the central nervous system, breast, colon, ovaries, kidneys, lung, bladder, prostate and head and neck.

More specifically, the arsenic compounds of the present invention can be used to treat tumors of epithelial origin including but not limited to:

- squamous cell carcinoma
- basal cell carcinoma
- melanoma

- tumors of epithelial lining of glands or ducts:
adenocarcinoma
papillary carcinoma
papillary adenocarcinoma
- 5 tumors of the liver and biliary tract:
Hepatocellular carcinoma
- tumors of the gastrointestinal tract:
squamous cell carcinoma of the esophagus
adenocarcinoma of the esophagus
10 colorectal carcinoma (colon cancer)
gastric carcinoma (stomach cancer)
- tumors of respiratory tract:
bronchogenic carcinoma
small cell carcinoma
15 large cell carcinoma
- tumors of the urogenital tract:
transitional cell carcinomas of bladder
squamous cell carcinoma of bladder
carcinoma of prostate
20 carcinoma of cervix
- tumors of breast
tumors of blood cells and related cells (leukemias):
acute and chronic lymphocytic leukemia
polycythemia vera
- 25 Cancers of Lymphoid tissue
Malignant Lymphomas - Hodgkins Lymphoma
Non-Hodgkin's Lymphoma- Follicular lymphoma
Diffuse lymphoma
Small lymphocytic lymphoma
- 30 Large cell lymphoma
Lymphoblastic lymphoma
Multiple myeloma
- Tumors of Connective Tissue
Cancers of Bone
35 Osteosarcoma
- Tumors of the Nervous System
Neuroblastoma

34 34

carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma; leukemias, e.g., acute lymphocytic leukemia (myeloblastic, promyelocytic, myelomonocytic, monocytic and erythroleukemia); chronic leukemia and chronic lymphocytic leukemia; and polycythemia vera, lymphoma (Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenström's macroglobulinemia, and heavy chain disease. Alternatively, it can be labeled for treatment of the appropriate infectious disease.

Alternatively, pharmaceutical compositions may be formulated for treatment of appropriate infectious diseases.

If the complex is water-soluble, then it may be formulated in an appropriate buffer, for example, phosphate buffered saline or other physiologically compatible solutions. Alternatively, if the resulting complex has poor solubility in aqueous solvents, then it may be formulated with a non-ionic surfactant such as Tween, polyethylene glycol or glycerine. Thus, the compounds and their physiologically acceptable solvates may be formulated for administration by inhalation or insufflation (either through the mouth or the nose) or oral, buccal, parenteral, topical, dermal, vaginal, drug delivery device, e.g., porous or viscous material such as lipof foam, rectal administration or, in the case of tumors, directly injected into a solid tumor.

For oral administration, the pharmaceutical preparation may be in liquid form, for example, solutions, syrups or suspensions, or may be presented as a drug product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents

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(e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters, or fractionated vegetable oils); and preservatives (e.g., methyl or propyl-p-hydroxybenzoates or sorbic acid). The pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinized maize starch, polyvinyl pyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulphate). The tablets may be coated by methods well-known in the art.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, e.g., gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Such formulations are sterile. Formulations for injection may be presented in unit dosage form, e.g., in ampules or in multi-dose containers, with an

added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

- 5 Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

10 The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

15 In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophilic drugs.

25 The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration.

30 The invention also provides kits for carrying out the therapeutic regimens of the invention. Such kits comprise in one or more containers therapeutically effective amounts of the arsenic compounds in pharmaceutically acceptable form. The arsenic compound in a vial of a kit of the invention may be in the form of a pharmaceutically acceptable solution, e.g., in combination with sterile saline, dextrose solution, or buffered solution, or other

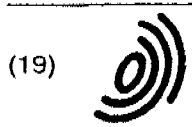
vinblastine, methotrexate, hydroxyurea, cyclophosphamide, doxorubicin, 5-fluorouracil, taxol, diethylstilbestrol, VM-26(vumon), BCNU, all-trans retinoic acid, procarbazine, cytokines, therapeutic vaccines, and other immunomodulators.

17. The method of claim 1, 2, 3 or 12 in which said administration is made via an implantation device.

18. A method of treating hematopoietic disorders in a mammal which comprises administering one or more arsenic compounds to said mammal, wherein said hematopoietic disorder is selected from the group consisting of acute lymphocytic leukemia, chronic lymphocytic leukemia, hairy cell leukemia, myeloid metaplasia, myeloid dysplastic syndrome, multiple myeloma and plasmacytoma.

19. An oral pharmaceutical composition useful for treating neoplastic diseases in a human which comprises an effective amount of an arsenic compound or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

20. A sterile unit dosage form adapted for parenteral administration which comprises a therapeutically effective non-lethal amount of arsenic trioxide in an aqueous carrier, said dosage form being contained in a sealed sterile glass container.



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European Patent Office
Office européen des brevets



(11) **EP 0 804 928 A1**

(12)

EUROPEAN PATENT APPLICATION

published in accordance with Art. 158(3) EPC

(43) Date of publication:
05.11.1997 Bulletin 1997/45

(51) Int. Cl.⁶: **A61K 33/28**, A61K 33/36

(21) Application number: 94920596.7

(86) International application number:
PCT/RU94/00128

(22) Date of filing: 15.06.1994

(87) International publication number:
WO 95/22336 (24.08.1995 Gazette 1995/36)

(84) Designated Contracting States:
CH DE FR LI

(30) Priority: 18.02.1994 RU 94004903
18.02.1994 RU 94004904

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(54) **AGENT HAVING AN IMMUNOMODULATING EFFECT AND REDUCING DISTURBED FUNCTIONING OF THE TISSUE CELL PROPAGATION REGULATING SYSTEM**

(57) An agent having an immunimodulating effect and reducing disturbed functioning of the tissue cell propagation regulating system consists of an active substance which is mercury dichloride or potassium arsenite or sodium arsenite, in a quantity of 0.05 to 1.5 wt. % and a diluent to make up 100 wt. %. The diluent used in the said agent preferably contains grape white wine with a sugar content of 3-4 wt. % or milk whey with a sugar content of 3-4 wt. %.

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Description

Field of the Invention

The present invention relates to medicine and, more particularly, it relates to novel immunomodulator having regenerating effect on abnormal function of cell tissue division-regulating system.

Description of the prior art

Known in the art is a variety of immune response-modulating agents. Thus for example, the capacity of stimulating immune responses in the body (including leukopoiesis) exhibits nucleic acid derivatives; the capacity of activating specifically immunocompetent cells (T and B-lymphocytes) have pyrogenal, prodigiosan and the like. It is well known that levamisole, (-) 2,3,5,6-tetrahydro-6-phenyl-imidazo[2,1-b]-thiazole hydrochloride can stimulate selectively the regulatory T-lymphocyte function, enhance poor reaction of cell-mediated immunity, suppress brisk antibody response, with it having no effects on normal reaction (M.D. Mashkovsky, "Pharmaceuticals", Moscow, "Medicine", 1992, V.2, p. 169-170).

There is also known in the art a medicinal agent, thymaline (complex of polypeptide fractions isolated from cattle thymus gland), which can regulate T and B lymphocyte production, stimulate the cell-mediated immune responses and promote regeneration processes (M.D. Mashkovsky, "Pharmaceuticals", Moscow, "Medicine", 1992 V.2, p. 171).

This medicinal agent is used as an immunostimulant and biostimulant in treatment of disorders associated with weakening the cell-mediated immunity including acute chronic purulent processes and inflammations, burn disease. It is also suited to use at conditions associated with suppression of immune and blood formation function in oncologic patients after a radiation therapy or chemotherapy.

However, all of the above-mentioned medicinal agents are faulty for their selective action, toxicity, a number of adverse effects and contradictions for administration.

It is well known by those skilled in the art that a key stage of tumor formation is associated with failure of cell division-regulating system.

There are a great variety of antineoplastic agents that are compounds having different chemical structures. Such compounds can be synthesized via chemical reactions or they can be prepared by isolation of biologically active substances from raw materials of vegetable and animal origin (M.D. Mashkovsky, "Pharmaceuticals", Moscow, "Medicine", 1992, v.2, pp. 423-468). Such antineoplastic agents include cyclophosphamide, sarcolysine, mustargen, caryolysine and the like. The alkylating properties of such agents are of considerable importance in mechanism of their action. They are capable of reacting with nucleophilic centers of protein molecules such that DNA synthesis is disturbed, resulting in abnormal vital activity of cells and inhibition of their mitotic division.

Known in the art are antineoplastic ethylenimine-containing agents such as thiophosphamide, dipine, benzoteph and the like which are compounds that have cytostatic and suppressive effect on proliferating tissue including malignant tissue.

The disturbance of nucleic acids metabolism and the blocking of mitotic cell division are of great concern in the mechanism of action of such medicinal agents.

Among antineoplastic agents, a few of antibiotics are in wide use, more particularly semi-synthetic derivatives wherein nuclei of molecules from the known antitumor antibiotics are used. The effector mechanism of such medicinal agents is associated with selective inhibition of DNA-dependent RNA synthesis, resulting in disturbance of nucleic acid production.

However, most of antitumor agents mentioned above are faulty for their high toxicity, adverse effects (suppression of blood formation). No antineoplastic agents which could regenerate the defective function of cell tissue division-regulating system has previously been reported.

Mercury-containing compounds are widely used in medicine as antiseptics, such as mercury dichloride. Known in the art is the use of arsenic-containing preparations (sodium arsenate and potassium arsenite) for treatment of patients suffered from hematological diseases due to their capacity of inducing bone marrow erythropoiesis and suppressing leukopoiesis.

However, the above-mentioned pharmaceuticals have not been proposed to use as an immunomodulating or regenerating agent in conditions associated with defective function of cell tissue division-regulating system.

Disclosure of the Invention

The invention is based on the problem of providing novel immunomodulating agent having a regenerating effect on abnormal defective function of cell tissue division-regulating system, high efficiency, low toxicity and wide spectrum of its action.

The problem is solved by providing a pharmaceutical formulation of the present invention, which has an immu-

nomodulating and regenerating effects on abnormal function of cell tissue division-regulating system, comprising an active ingredient and a diluent, with the active ingredient being mercury dichloride or potassium arsenite, or sodium arsenate, at the following mixture ratio, % by weight :

mercury dichloride or potassium arsenite or sodium arsenate	0.01 - 1.5
diluent	up to 100.0

A pharmaceutical formulation of the present invention includes preferably, as a diluent, dry white grape wine with sugar content of 3-4 % by weight or whey with sugar content of 3-4 % by weight.

The reversible coagulated vegetable proteins with released SH-groups of dry white grape wine and reversible coagulated proteins of whey, contained in small amounts, are blocked by mercury or arsenic ions, thereby eliminating toxicity of the proposed pharmaceutical formulation.

3-4 % content of sugars in the wine and whey assists to maintain acid fermentation medium and improves the gustatory quality of the proposed pharmaceutical formulation.

The preferred embodiments of a pharmaceutical formulation of the invention are as follows.

A pharmaceutical formulation of the invention for internal or external use contains the following ingredients, % by weight :

mercury dichloride	0.01 - 0.1
dry white grape wine with sugar content of 3-4 % by weight or whey with of sugar content of 3-4 % by weight	up to 100.0

A pharmaceutical formulation of the present invention for internal or external use containing as the diluent a mixture of pork fat, natural honey and ethyl alcohol, includes the following ingredients, % by weight:

mercury dichloride	0.03 - 0.13
pork fat	30.7 - 37,3
natural honey	30.7 - 37,3
ethyl alcohol	up to 100.0

A pharmaceutical formulation of the invention for internal use, which may be preferably used for treatment of acute and chronic leukosis, includes the following ingredients, % by weight :

sodium arsenate or potassium arsenite	0.05 - 0.15
dry white grape wine with 3-4 % sugar content or whey with 3-4 % sugar content	up to 100.0

The use of such pharmaceutical formulation of the present invention is preferable for treatment of acute and chronic leukosis, since the main depot of arsenic accumulation is blood.

A pharmaceutical formulation of the invention for external use includes the following ingredients, % by weight :

mercury dichloride	0.3 - 1,5
dry white grape wine with 3-4 % sugar content or whey with 3-4 % sugar content	up to 100.0

present in small amounts in wine product, resulting in release of protein SH-groups that are reversibly protected with mercury or arsenic ions. This makes the solution non-toxic.

The whey also contains coagulated proteins with released SH-groups to be protected reversibly by mercury or arsenic ions. This makes the toxicity of the solution reduce to zero.

A pharmaceutical formulation of the invention can be recommended for treatment of the following diseases: all types of innocent tumors; all types of malignant tumors; various immunodeficient conditions; rheumatism; rheumatoid arthritis; polyarthritis; bronchial asthma; systemic lupus erythematosus; gastric ulcers; gravitational ulcers; herpes; psoriasis; intestinal infection; neurodermite and the like.

The choice of appropriate pharmaceutical formulation of the invention and the duration of its administration can vary from the form and duration of disease, the drug tolerance and other individual peculiarities of patient's body, whereas one should follow a few of requirements during the treatment. For example, one should keep some diet restrictions with excluding such food products as meat, fish, eggs, since during the treatment with a pharmaceutical formulation of the invention there occur the protection of SH- groups in the system of proteolytic enzymes, that is to say the capabilities of the organism to digest protein food become low.

Usually, the course of treatment includes the administration of the proposed pharmaceutical formulation per os according to following regimen: the first three days - 5 ml (or 5 g) 3 times a day, then 10 ml (or 10 g) for one month 3 times a day. Simultaneously with or without oral administration, the pharmaceutical formulation may be preferably used as lotions, tampons, syringings and enemas. The appropriate locus to be treated is chosen depending on the localization of a pathologic process, with the proposed formulation applied to coccygeal bone, groin lymph nodes, axilla, backbone, joints, localized neoplasms, integumentary or bone-joint tissues. Thus for example, in treatment of mammary gland or female genitals, a pharmaceutical formulation of the invention, along with oral administration, may be used as lotions and vaginal tampons, as well as enemas. In treatment of stomach disorders a pharmaceutical formulation of the invention, along with oral administration, may be applied as lotions to axilla and coccygeal bone and enemas, as well. In treatment of adenoma, a pharmaceutical formulation of the invention, along with administration per os, should locally be applied as lotions to coccygeal bone, groin and axillary lymph nodes. In myeloid leukemia, along with oral administration, the proposed pharmaceutical formulation is given per os and applied as lotions to coccygeal bone, chest, groin and axillary lymph nodes, backbone, articulations.

In treatment of soft tissue damages and osteogenic sarcoma a pharmaceutical formulation of the invention, along with oral administration is preferably applied locally as lotions to coccygeal bone, groin and axillary areas, backbone.

A pharmaceutical formulation of the invention with increased mercury content is used for treatment of pulmonary malignant diseases with pus and blood in the sputum.

A pharmaceutical formulation of the invention comprising mercury dichloride as the active ingredient showed to advantage in treatment of skin disorders such as psoriasis and neurodermite. This is most likely to be associated with immune response- modulating properties of a pharmaceutical formulation of the invention which, when externally used, exhibits also an antiinflammatory and repairing effects.

The use of a pharmaceutical formulation of the invention, comprising mercury dichloride as the active ingredient in treatment of gravitational ulcers showed the improvement under administration of the preparation per os following the general regimen together with applying it locally as lotions. The duration of treatment course is 1 month. The treatment, if required, may be repeated in 1 month.

A pharmaceutical formulation of the invention is prepared by conventional methods by mixing the starting materials

A pharmaceutical formulation of the invention was studied in experiments on animals and tested clinically in human beings.

The test for acute toxicity of a pharmaceutical formulation according to the invention was conducted on 192 healthy male unbred rats (body weight of 180-220 g) under standard conditions of feeding and keeping. 24 hours before and during the study, the test animals were kept under constant temperature and air ventilation in vivarium. 2 hours prior to the start of the study the animals were deprived of water and food.

The acute toxicity (LD₅₀) for each pharmaceutical formulation of the invention to be administered orally or intraperitoneally to provide high toxic effect was determined by the Litchfield-Wilcoxon method.

By weighing and screening animals, there were selected 10 rat groups, which were given a pharmaceutical formulation of the invention (liquid forms including dry white wine or whey). Each group included 6 animals.

Rat groups were given intraperitoneally 5; 4; 3; 2 and 1 ml of the proposed pharmaceutical formulation, which amounts corresponded to the following doses of an active ingredient - 1.65; 1.32; 0.99; 0.66 and 0.33 mg/kg. In addition, the proposed pharmaceutical formulation was administered orally to the test animals in amounts of 2; 1.5; 1 and 0.5 ml that corresponded to the following doses of the active ingredient - 0.66; 0.495; 0.33 and 0.165 mg/kg. Control animals were given appropriate diluents, namely, dry white grape wine or whey.

The test animals were under observation for 14 days after the treatment with the proposed pharmaceutical formulation. To this end, the evaluation of the general condition, behavior and body weight of test animals was conducted.

Upon administering the proposed pharmaceutical formulation in the above-indicated doses, there was observed

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duction of the circulating antibodies was observed. With multidirectional character of changes in the other immunologic performances, it should be noted that such values are within the physiological norm.

The same picture was observable under examination of the immunologic performances in the the patients after the 2-3 month-period treatment prior to the second course of the therapy with the proposed formulation. During the repeated course, different changes in the immunologic performances in the patients were the same as those observed in the the first course of the treatment, but they had no single-sided direction in all of the patients. We tried during the study to unify patients into the groups according to the types of the changes, to link such changes to the blood groups, however, our attempts to reveal the strict regularities was unsuccessful.

The improvement of all of the studied performances in the patients was observable 6 months later after the 2-3 course treatment using the proposed pharmaceutical formulation. The comparison of the data obtained from the clinical trials concerning the immunotropic properties of the proposed pharmaceutical formulation showed a high specific character of the immune reaction in each patient. In general, the reaction undergoes the two phases. The first phase is characterized by the undirectinal changes in immunologic performances. Apparently, reconstruction of the internal regulatory mechanisms, combining immune cells into the single system, takes place under the effect of the declared agent. The second phase is associated with the normalization of the immunologic performances. Here, the general effects are as follows: decrease of the level in circulating immune complexes; the normalization of the helpers suppressor cell ratio of their subpopulation. The both phenomena are beneficial for the prognostic value, as they is indicative of returning the immunological state to norm. The decrease in the level the circulating immune complexes is observed in all of the oncologic patients and the subjects suffered from the rheumatoid arthritis. In addition, the normalization in ratios of the lymphocyte subpopulations is characteristic of the most of the patients of such groups.

The proposed pharmaceutical formulation was studied clinically in more than 250 patients. The preparation was tested in the treatment of the following diseases: malignant and innocent tumors, rheumatism, rheumatoid arthritis, bronchial asthma, neurodermitis and the like.

The main oncologic diseases were: female organs illnesses (cancer of mammary gland, carcinoma of uterine cervix and corpus, cancer of ovaries), diseases of hematopoietic system (lymphogranulomatosis, lymphoid leukosis, myelogenous disease), diseases of the internal organs and tissues (cancer of rectum, carcinoma of the stomach, liver, cancer of the rhinopharynx, skin and the like); among the innocent tumors such as prostate adenoma, uterus fibromyoma, mammary mastopathy, cyst, rectal polyp and the like.

The patients were at the age of 20 - 60 year; the duration of treatment with the proposed pharmaceutical formulation was of 0.5 to 2 years and more.

A pharmaceutical formulation of the present invention was used according to the method given above: internal use - first three days 5 ml 3 times a day, then 10 ml x 3 times a day for one month. Along with the administration per os, the proposed pharmaceutical formulation was applied locally depending on the pathological locus of the disease. The pharmaceutical formulation of the invention was applied locally to the pathologic locuses as lotions, tampons, syringings, enemas. The formulation was applied on the appropriate areas to be treated, including coccygeal bone, groin lymph nodes, axilla, backbone, joints, localized neoplasms, integumentary or bone-articular tissues.

The data of the treatment with using the proposed pharmaceutical formulation including including oncologic patients of stages IV, III, II (with the duration of patient's treatment varied from more than 0.5 year, more than 1 year, more than 2 years) as well the subsequent long-term supporting therapy with such formulation showed its efficiency in both untreated and prereated patients.

It was observable the complete regression of a new growth (malignant tumor), depending on the disease type, its stage and the duration of the treatment in 34,3% of patients; in 80.8 % of patients with innocent tumors. In some patients stabilization of the process, decrease in tumor size were observed. An improvement of general condition was revealed in all the patients.

For a better understanding the present invention, some specific examples illustrating the preparation and clinical studies of the proposed pharmaceutical formulation are given hereinafter.

Example 1.

A pharmaceutical formulation containing the following ingredients:

mercury dichloride	0.01 g
white grape wine with 4% sugar content	110 ml

The proposed pharmaceutical formulation is prepared by the method as follows. Mercury dichloride is dissolved in dry grape wine in given amounts at conventional conditions (at room temperature) to give a clear light-yellow solution

mercury dichloride	0.25 g
pork fat	230 g
natural honey	240 g
96 °alcohol	up to 750 g

The pharmaceutical formulation is prepared by the method as follows:

Mercury dichloride is dissolved in ethyl alcohol. Preliminary softened pork fat is mixed with natural honey in given amounts. Thereafter, the solution of mercury dichloride in ethyl alcohol is added in small portions to a mixture of pork fat with honey with rubbing carefully. The proposed pharmaceutical formulation is obtained as light-yellow creame-like product. The preparation is suitable for internal and external use.

Example 7.

The pharmaceutical formulation containing the following ingredients:

potassium arsenite	0.05 g
dry white grape wine with 4 % sugar content	up to 100 ml

The pharmaceutical formulation is prepared by dissolving of potassium arsenite in dry white grape wine in given amounts. There is obtained a clear light- yellow cream solution, pH 3.2. The preparation is suitable for administration per os.

Example 8.

A pharmaceutical formulation containing the following ingredients:

sodium arsenate	0.15
whey with 3 % sugar content	up to 100 ml

The pharmaceutical formulation is prepared by dissolving of sodium arsenate in whey with sugar content of 3 % by weight in a given amounts. A clear solution of light-yellow colour is obtained.

The preparation is suitable for local application.

Example 9.

The pharmaceutical preparation was tested clinically in 99 oncologic patients, of them: 67 subjects have malignant tumors, 32-innocent tumors. Of the first group, 32 patients underwent a course of pretreatment (surgical operation, multiple chemotherapy, gamma-therapy), 35 - were not given the treatment earlier.

In most of the oncologic patients there was noted : IV stage of disease in 21 subjects, III stage of disease in 18; II stage was in 6 patients. In 22 patients the disease stages were not identified.

The oncologic patients were at the age of 40 to 60 - 39 subjects; 20 to 40 - 7 subjects; more than 60 - 14 subjects. The patients were 11 males and 56 females.

The terms of the patients treatment with the proposed pharmaceutical formulation were the following: more than 0.5 years - 28 patients (41.8 %), more than 1 year - 3 patients (4.5 %), more than 2 years - 19 patients (28.3 %). Long-term supporting therapy with a pharmaceutical formulation was conducted in 17 patients (25.4 %). The basic diseases were the following: malignant tumors (cancer of the mammary gland, carcinoma of uterine cervix and corpus, cancer of ovaries, cancer of rectum, carcinoma of the stomach, liver, cancer of rhinopharynx, skin); diseases of the hematopoietic system (lymphogranulomatosis, lymphoid leukosis, acute lymphoblastic leukemia, myelogenous disease); innocent

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

202075

Bogotá, D.C., (06 de Diciembre de 2007).

Abogado

MAURICIO JARAMILLO CAMPUZANO

ASUNTO

Radicación 04112812
Trámite 002
Evento 001
Actuación 430
Oficio 16812
Folios 022

Patente de Invención

☒

Patente de Modelo de Utilidad

☐

Vía Nacional

☐

Vía PCT (fase nacional)

☐

Cap. I

☐

Cap. II

☒

No. Sol. Internacional

PCT/NL02/00231

Fecha de Presentación Interna.

10 de Abril de 2002.

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

- 1.1. Descripción: Folios: 18 a 20 (como se radicó inicialmente)
- 1.2. Reivindicaciones: Folio : 21 (como se radicó inicialmente)

2. Objeto de la invención

- Título de la solicitud: Composición farmacéutica que comprende arsenito para el tratamiento de malignidad.

El objeto de la presente solicitud de patente de invención consiste en:

Una composición farmacéutica que contiene arsénico .

Reivindicaciones 1-3

: Composición farmacéutica a base de una sal de meta-arsenito

Reivindicaciones 4-5

: De uso.

Reivindicación 6

: Método de tratamiento.

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El problema planteado en esta solicitud es la necesidad una composición farmacéutica apta para terapias contra el cáncer, que permita el tratamiento de tumores sólidos.

Para solucionar este problema técnico la solicitud en estudio proporciona una composición farmacéutica a base de arsénico.

El objeto de la invención definido anteriormente se clasifico de acuerdo con la Clasificación Internacional de Patentes (IPC) : A61K33/36, A61P35/00.

3. De la solicitud de Patente

3.1. Descripción (artículo 28 D. 486)

Teniendo en cuenta la definición de la composición farmacéutica del folio (21) , esta Dependencia se permite señalar que dentro del aparte descriptivo lo único que se encuentra es una descripción del objeto del invento, en que tipo de tumores se utiliza y las sales de preferencia utilizadas (folios 18-19).

Adicionalmente se encuentra un ejemplo para realizar la prueba de citotoxicidad en donde no se muestra la concentración del activo utilizada y los datos obtenidos de dicha prueba, los cuales no muestran un efecto inesperado ya que se encuentran afectados por el estado de la técnica (Cuadro 1) (Folios 19-20).

Al revisar el capítulo descriptivo, en ninguna parte se muestra la composición farmacéutica que se reivindica (formas farmacéuticas posibles, composiciones, auxiliares, contenido de activo entre otras . Adicionalmente la descripción se encuentra enfocada principalmente , a el uso de dichos derivados de arsénico para el tratamiento de malignidades.

En consecuencia, las reivindicaciones 1-3 no encuentran sustento dentro del aparte descriptivo de la solicitud

Se requiere al solicitante ajustar su capítulo descriptivo y reivindicatorio de acuerdo a aquellas modalidades que son objeto de la invención y a las observaciones realizadas, teniendo cuidado de no ampliar la materia más allá de cómo se estableció originalmente.

4. Excepción a la patentabilidad (artículo 20 D486 literal a)-d))

Se aclara que, de acuerdo al Art 20 literal d) el método terapéutico de la reivindicación 6 no es patentable.

5. Reivindicaciones relativas a un uso o a un segundo uso (artículos 14 y 21 D 486)

Se aclara que, de acuerdo con el Art 14, no se puede otorgar patente al uso de las reivindicaciones 4-5 , porque no es un producto ni un procedimiento tecnológico.

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6. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual su fecha de presentación internacional es 10 de Abril de 2002, se consultaron las bases de datos y los archivos con que cuenta la entidad con fecha de publicación anterior y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud :

Nº	Documento	Título	Fecha de publicación*
D1	WO9918798	Compositions and methods for the treatment of primary and metastatic neoplastic diseases using arsenic compounds.	22 de Abril de 1999.
D2	EP0804928	Agent having an immunomodulating effect and reducing disturbed functioning of the tissue cell propagation regulating system.	05 de Noviembre de 1997.

7. Análisis de patentabilidad (artículo 14 D486)

7.1. Novedad (artículo 16 D486)

Comparando elemento por elemento el objeto de esta solicitud con lo mencionado en las anterioridades, tenemos que:

La presente Solicitud de Patente Colombiana No. 04112812 , se refiere a:

Una composición farmacéutica a base de arsénico farmacéutica apta para terapias contra el cáncer, que permita el tratamiento de tumores sólidos.

D1 (Folios 77-87) composiciones farmacéuticas a base de sales de arsenito que son útiles en el tratamiento de tumores solidos (cólon, renal, ovarios, entre otros).

“ (Si se trata de un complejo soluble en agua este puede ser formulado en un buffer apropiado por ejemplo buffer salino de fosfato y otras soluciones fisiológicamente compatibles. Alternativamente si el complejo resultante tiene pobre solubilidad en solventes acuosos , entonces puede ser formulado con un surfactante como tween, polietilenglicol o glicerina .”

Para administración oral las preparaciones farmacéuticas pueden ser en forma líquida, por ejemplo soluciones, jarabes o suspensiones o puede ser reconstituido con agua u otro vehículo apropiado. Se pueden utilizar agentes suspensores como (sorbitol, derivados de celulosa) agentes emulsificantes (como lecitina y acacia) y vehículos no acuosos (aceites vegetales).

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Las tabletas o cápsulas pueden ser preparadas con almidón, polivinilpirrolidona, lactosa, celulosa microcristalina, estearato de magnesio, lauril sulfato etc...)"

Estas composiciones específicas de la anterioridad D1 (Folios 84 líneas 17-37, Folios 85-86 y Folio 87 líneas 19-29) son iguales a las composiciones farmacéuticas de la presente solicitud

Como se observa, el elemento característico de la composición farmacéutica reivindicada en 1-3 era conocida en D1 y está comprendido en el estado de la técnica, con lo cual se considera que NO cumple con el requisito de Novedad.

D2 (Folios 88-93) enseña composiciones farmacéuticas que contienen un agente con efecto inmunomodulador que regulan la propagación de células y son útiles en el tratamiento de todos los tipos de tumores malignos entre ellos (cáncer de glándulas mamarias, carcinoma de cuello uterino, cáncer de ovarios etc..)

Arsenito de potasio	0.01-1.5
diluyente	Para 100.0

Arsenito de potasio	0.05-0.15
Vino de uva blanco seco con 3-4 % de Azúcar o suero con 3-4% contenido de azúcar.	Para 100.0

Arsenito de potasio	0.05 g
Vino de uva blanco seco con 4 % de Azúcar	Para 100.0 mL.

Estas composiciones específicas de la anterioridad D2 (Folio 90 líneas 5-6 líneas 45-46, Folio 93 líneas 23-24) son iguales a las composiciones farmacéuticas de la presente solicitud

Como se observa, el elemento característico de la composición farmacéutica reivindicada en 1-3 era conocida en D1 y está comprendido en el estado de la técnica, con lo cual se considera que NO cumple con el requisito de Novedad.

8. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento Nº	Reivindicaciones afectadas	Requisito que afecta
D1	WO9918798	1-3	Novedad.
D2	EP0804928	1-3	Novedad.

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En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha _____ 1997

CONCEPTO TÉCNICO No. 2492	EXAMINADOR TÉCNICO Código No.202075
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