

Q F



Industria y Comercio
SUPERINTENDENCIA

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

PCT
SOLICITUD

PATENTE DE INVENCION

05-74439

21. EXPEDIENTE No.

54. TITULO COMPRIMIDO RECUBIERTO CON PELICULA QUE COMPRENDE UN
EXTRACTO DE HOJAS DE PARRA

51. CLASIFICACION INTERNACIONAL A61K9/28 ; A61K35/78
A61P43/00

71. SOLICITANTE BOEHRINGER INGELHEIM INTERNATIONAL GMBH

DOMICILIO Ingelheim, República Federal de Alemania.

74. APODERADO EMILIO FERRERO

.C.C 438.019 de Usaquén.

22. BOGOTA, D.C., 28/07/2005.

SS



Industria y Comercio
SUPERINTENDENCIA

PETITORIO

SUPERINTENDENCIA Y COMERCIO

Radicación: 05074479 CIRC 2223

Folios: 181 ición

Fecha (PCT): 2003-07-20 17:32:38

Tratado: 811 PCT-PATENT 379 FASE NACI 411 PRESENTAC

Dependencia: 2320 DIVISION DE NUEVAS CREACIONES

FORMULARIO UNICO DE SOLICITUD DE PATENTE PCT

ENTRADA EN FASE NACIONAL 31-07-05

SOLICITUD DE:

1

☒ Patente de Invención.
☐ Capítulo I.

☐ Patente de Modelo de Utilidad.
☒ Capítulo II.

2

**SOLICITANTE
(71)**

Nombre: **BOEHRINGER INGELHEIM
INTERNATIONAL GMBH**
sociedad constituida y existente bajo las
leyes de la República Federal de Alemania

Dirección: Binger Strasse 173,
55216 Ingelheim,
República Federal de Alemania
Domicilio: Ingelheim,
República Federal de Alemania

IDENTIFICACIÓN

C.C. ☐ NIT ☐
C.E. ☐ Otro ☐
Cual _____
Número _____

3

**REPRESENTANTE
O APODERADO**

Nombre: **EMILIO FERRERO**
Dirección: Carrera 4ª. No. 72-35
Teléfono: 347 38 11
Fax: 211 88 50
E-mail: clientes@camyo.com.
Domicilio: Bogotá, Colombia.

IDENTIFICACIÓN

C.C. ☒ NIT ☐
C.E. ☐ Otro ☐
Cual _____
Número 438.019 T.P 31.929

4

**INVENTOR (ES)
(72)**

1. Anke **ESPERESTER**
Rosmerthastrasse 84,
55216 Mainz,
República Federal de Alemania
3. Fritz **SACHER**
Kaiser-Karl-Strasse 27,
55435 Gau-Algesheim,
República Federal de Alemania

2. Eckhard **SCHAEFER**
Richard-Wimmer-Strasse 23,
63150 Heusenstamm,
República Federal de Alemania

5

PCT (86)

Solicitud Internacional No. PCT/EP2003/014148

Fecha: 12 de Diciembre de 2003

Publicación Internacional No. WO 2004/058227 A1

Fecha: 15 de Julio de 2004

6

Título (54)

**COMPRESO RECUBIERTO CON PELÍCULA QUE
COMPRENDE UN EXTRACTO DE HOJAS DE PARRA**

7

Clasificación Internacional (51) A61K 9/28

A61K 35/78

8

Prioridad

SI ☒ NO ☐

(33) País de Origen

EP
EP

(32) Fecha

31 de Diciembre de 2002
5 de Septiembre de 2003

(31) Número de Solicitud

02029108.4
03019636.4

9

Comprobante de pago No.: 05 - 53.296

Fecha: 18 de Julio de 2005

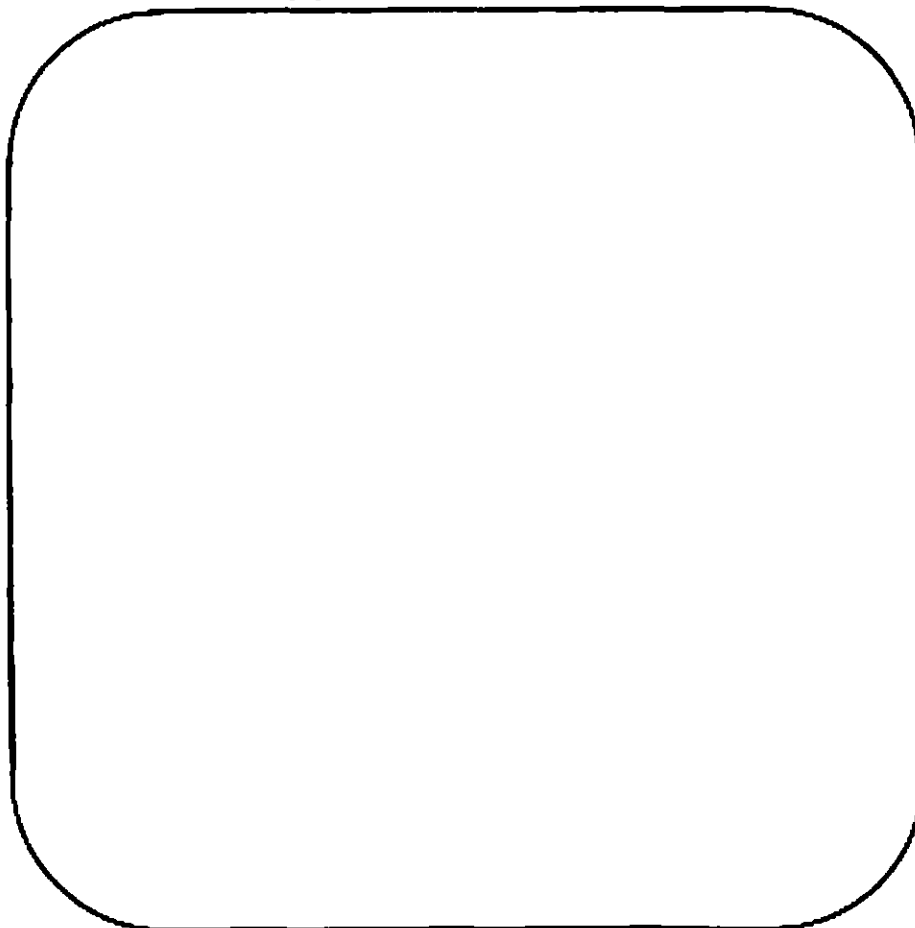
10

Anex s:

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por \$ 443.000.00.
- ☐ Comprobante de pago por reivindicación de prioridad.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☒ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros: VER HOJA DE DOCUMENTOS ANEXOS

11

FIGURA CARACTERÍSTICA



12

Solicito la concesión de la patente,

NOMBRE: EMILIO FERREROFIRMA: 

C.C. 438.019 de Usaquén T.P. 31.929

PRP

DOCUMENTOS ANEXOS

1. ☒ **Publicación Internacional WO 2004/058227 A1**

Descripción:

Páginas 1-21 en el idioma original

Páginas ____ en español

Reivindicaciones: Número (s) 1-16

Figuras: Número (s) 1-3

2. ☒ **Forma PCT/RO/101. PCT Request**
3. ☐ **Forma PCT/RO/106. Invitation to Correct Defects.**
4. ☐ **Forma PCT/ISA/210. Informe de Búsqueda Internacional.**
5. ☐ **Forma PCT/ISA/220. Notificación De La Transmisión Del Informe De Búsqueda Internacional Y De La Opinión Escrita De La Administración Encargada De La Búsqueda Internacional, O De La Declaración.**
6. ☐ **Forma PCT/ISA/237. Opinión Escrita De La Administración Encargada De La Búsqueda Internacional.**
7. ☒ **Forma PCT/IB/304. Notification Concerning Submission Or Transmittal Of Priority Document.**
8. ☐ **Forma PCT/IB/306. Notification Of The Recoding Of A Change.**
Descripción De Modificación:

9. ☒ **Forma PCT/IB/308. Notice Informing The Applicant Of The Communication Of The International Application To The Designated Offices.**
10. ☒ **Forma PCT/IB/332. Information Concerning Elected Offices Notified Of Their Election.**
11. ☒ **Forma PCT/IPEA/401. PCT Demand**
12. ☒ **Forma PCT/IPEA/402. Notification Of Receipt Of Demand By Competent International Preliminary Examining Authority.**
13. ☐ **Forma PCT/IPEA/408. Written Opinion.**
14. ☒ **Forma PCT/IPEA/416. Notification Of Transmittal Of The International Preliminary Examination Report.**
15. ☒ **Forma PCT/IPEA/409. Informe Del Examen Preliminar Internacional.**
16. ☐ **Traducción Al Español Del Informe Del Examen Preliminar Internacional.**
17. ☐ **Traducción Al Español De Los Anexos Presentados Junto Con El Informe Del Examen Preliminar Internacional.**



CONSULADO GENERAL DE COLOMBIA

MUNICH

Nr. 169

El Cónsul General de Colombia

CERTIFICA

Que el Dr. Hanns Paul Tüttenberg -----, quién autentica la firma del signatario en el presente documento, ejercía en la fecha allí indicada las funciones de Presidente del Tribunal Regional en Mainz.

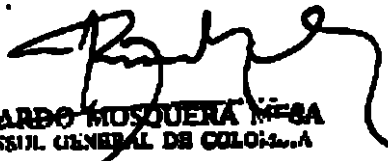
Que la firma BOEHRINGER INGELHEIM INTERNATIONAL GmbH, domiciliada en 55216 Ingelheim am Rhein, Registro Mercantil Nr. HR B 1063 del Juzgado Municipal de Bingen está constituida y ejerce su objeto social de conformidad con las leyes de la República Federal de Alemania.

Que los señores Dr. DIETER LAUDIN y Dr. GERHARD HUBER

quien(es) firman el presente documento tiene(n) facultad legal suficiente para representar a la mencionada firma y otorgar poderes en su nombre.

Que ha tenido a la vista la documentación que prueba lo anterior.

Munich, 18 de Diciembre de 1995


RICARDO MOSQUERA MESA
CONSUL GENERAL DE COLOMBIA



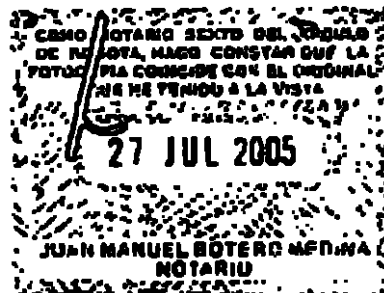
Derechos para la Nación
Fondo Rotatorio
Tasa consular

US \$ 6.-

US \$ 100.-

US \$ 1 x DM 1,60 = DM 169.60

PAGADO





MINISTERIO DE RELACIONES
EXTERIORES
BOGOTÁ

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[Handwritten signature]

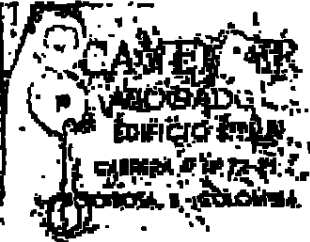
SECRETARÍA DE BOGOTÁ D.C.

ENE - 4 A 11: 44

RESPONSABILIDAD DEL TEXTO

COMO NOTARIE CERTIFIQUE EL
A LAJOTA HAGO CONSTAR QUE
FOTOCOPIA CANCELO CON EL DIFUNDO
USE DE TENDON A LA VISTA
27 JUL 2005
JUAN GABRIEL POTERO MELINA
NOTARIO

1045133 1027



REPRESENTACION Y PODER

For patents, utility models, industrial designs, trademarks, commercial names, trade emblems, slogans.

Para patentes, modelos de utilidad, diseños industriales, marcas de fábrica, nombres comerciales, enseñas, lemas comerciales.

REPRESENTATION AND POWER OF ATTORNEY

9253
0569

I (we), the undersigned / Yo (nosotros), abajo firmado (s)
BOEHRINGER INGELHEIM INTERNATIONAL GMBH

of / domiciliado (s) en **D-55216 Ingelheim am Rhein, GERMANY**

por el presente nominamos a GERMAN CAVELIER, rpa. 452; GONZALO PERDOMO, rpa. 881; EMILIO FERRERO, rpa. 31929 y LUZ CLEMENCIA DE PAEZ, rpa. 28555; domiciliados en la Carrera 4ª N° 72-33, Bogotá, Colombia, en obediencia a lo dispuesto en el parágrafo 1º del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestras) representantes en todos los asuntos de propiedad industrial con facultad para recibir notificaciones y comparecer apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquél. La misma regla se aplicará cuando el segundo representante suplente haya de reemplazar al primero, o al tercero al segundo, o al segundo suplente, en su caso, o ambos, declarando su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Consul de Colombia, en el extranjero; y al ser tratado de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare definitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primera o segundo suplente, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, sumisoriendo por el acto hecho de ejercerla, cuando en ese momento el ejercicio de la representación por el primero, segundo o tercer suplente en su caso.

Además, conferimos (conferimos) poder a los abogados arriba nominados, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que mis (nos) comparezcan ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, y diseños industriales; el registro de marcas de fábrica, colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, variedades vegetales y denominaciones de origen; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Las acciones de competencia desleal, protección del consumidor, oposiciones u observaciones, cancelación administrativa y judicial, nulidad, medidas cautelares, concesión de licencias, la tutela, la protección de secretos industriales, y en general los juicios civiles, penales, administrativos o contencioso-administrativos relacionados con estos derechos; acciones y procesos que promovamos o se nos promuevan. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistirse, cancelar, recibir, responder, y ratificar los actos de agentes oficiales.

in due compliance with the terms of paragraph 1st of article 543 of the Commercial Code, do hereby appoint GERMAN CAVELIER, rpa. 452; GONZALO PERDOMO, rpa. 881; EMILIO FERRERO, rpa. 31929; and LUZ CLEMENCIA DE PAEZ, rpa. 28555; domiciled at Carrera 4ª N° 72-33, Bogotá, Colombia, the first as principal, and the others as alternates, in the order of their appointment, as our representatives for all industrial property matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second alternate representative is to replace the first one, or when the third is to replace the first or second alternates in their turn, or both of them, second. In such cases, the principal representative, or the first or second alternates in their turn, or both of them, shall state their intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Consul abroad; and in case of impediment, the appropriate certificate shall suffice. If any of the appointees were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative, or of the first or second alternate in their turn ceases, the representation can be taken again in their sequence, by the principal, the first or second alternate depending on case, and the mere fact of its exercise will suffice. The exercise of the representation by the first, second or third alternates in their turn shall end at such time.

In addition, we grant a Power of Attorney in favor of the above-named attorneys-at-law so that they may obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models and industrial designs; the registration of trademarks, collective, defensive and service marks, slogans, commercial names, trade emblems, vegetal varieties and denominations of origin; its renewal, assignment, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b) Actions of unfair competition, protection to the consumer, oppositions or observations, administrative or Court cancellation, nullity, infringement, granting of licenses; the action for writ mandamus, the protection of trade secrets, and in general the civil, penal, administrative or contentious-administrative suits relating to these rights; actions and processes that we promote or are promoted against us (us). And that in all the above matters, they may substitute this Power of Attorney, transact, admit the facts of the case, desist, cancel, receive, respond, resign and ratify acts done by representatives without a Power of Attorney.

Given and signed this / Dado y firmado en **Ingelheim am Rhein, 12.12.1995**

BOEHRINGER INGELHEIM
INTERNATIONAL GMBH

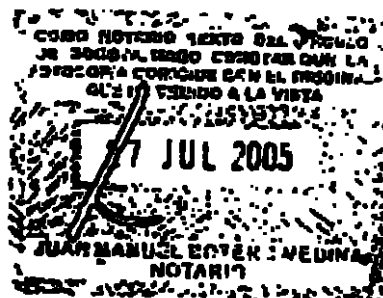
in/en ppa. ppa.
Dr. Dieter Laudien **Dr. Gerhard Huber**
Signature Firma

LEGALIZATION

El Señor Cónsul de Colombia debe expedir un certificado consular sobre (1) la existencia legal de la compañía que otorga el poder, (2) que ésta ejerce su objeto social, y (3) que las personas que otorgan el poder están autorizadas para darlo. A este efecto los señalamos que muestren al Señor Cónsul las pruebas que acreditan esos hechos (1), (2) y (3).

LEGALIZATION

The Colombia Consul must issue a consular certificate, the legal existence of the company which grants Power-of-Attorney, (2) that it is in actual exercise of company purposes, and (3) that the persons who execute Power of Attorney is authorized to do so. To this effect, please show the Consul the evidence to prove the above facts (1), (2) and (3).



NOTA PARA EL SEÑOR CONSUL DE COLOMBIA: Según los artículos 65 del C. de P.C. y 480 del C. de Co., si el poderdante es una sociedad, el Señor Cónsul debe certificar que tuvo a la vista las pruebas de su existencia, que ejerce su objeto social y que quien confiere el poder es su representante.

Vorseltige, vor mir gefertigte Namensunterschriften der Herren:

1. Dr. Dieter L a u d i e n, Dipl.-Chemiker, wohnhaft in 55127 Mainz,.
2. Dr. Gerhard H ü b e r, Rechtsanwalt, wohnhaft in 55411 Bingen,

- mir bekannt -

beglaubige ich hiermit.

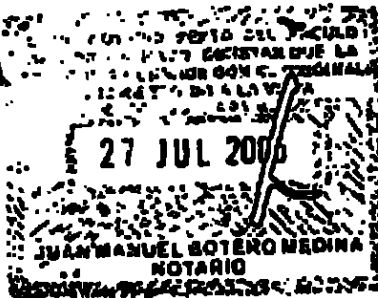
Gleichzeitig bescheinige ich aufgrund heutiger Einsichtnahme in das Handelsregister des Amtsgerichts Bingen, daß die Firma Boehringer Ingelheim International GmbH mit Sitz in Ingelheim am Rhein im Handelsregister des Amtsgerichts Bingen unter HR B 1063 eingetragen ist und daß die Herren Dr. Laudien und Dr. Huber als Prokuristen gemeinschaftlich zur Vertretung der Gesellschaft berechtigt sind.

Ingelheim am Rhein, den 12. Dezember 1995/hün


Notariatsverweser
anstelle des Notars
Prof. Dr. Weirich in Ingelheim



- 90) 1 -



Die Echtheit vorstehender Unterschrift des Notarassessors Dr. Peter Wirth - Notariatsverweser anstelle des Notars Prof. Dr. Weirich in Ingelheim und die Echtheit des beigedruckten Dienst - ~~stempel~~ - siegels werden hierdurch bestätigt. Zugleich wird bescheinigt, daß der Vorgenannte zur Vornahme der Amtshandlung gesetzlich befugt war.

Kostenabrechnung:

Gebühr für Legalisation

(Wert: DM 5,00,-)

JVKostO. v. 28.7.1987

BGBI. I S. 801

DM 5,00,-

12. DEZ 1995

Mainz, 12. DEZ 1995


Amtsnotar



Mainz, den dreizehnten Dezember neunzehnhundertfünfundneunzig
Der Präsident des Landgerichts


(Dr. Hans Paul Türlberg)

7

TRADUCCION OFICIAL No. 5133

de un documento escrito en Alemán, el cual para su identificación se sella con el sello de la traductora, lo mismo que lo presente.-

(A continuación del poder conferido a GERMÁN CAVALLIER, tpa. 837; SONISLO PERDOMO, tpa. 837; EMILIO FERRERO tpa, 31424; y LUZ CLEMENTIA DE PAEZ, tpa 2555- domiciliados en la Carrera 4 No. 72-30, Bogotá, Colombia, por la BÜHRINGER INGELHEIM INTERNATIONAL GMBH, domiciliada en C-53216 Ingelheim am Rhein, RFA, a través de sus representantes los Srs. Dr. Dieter Landien y Dr. Gerhard Huber.)

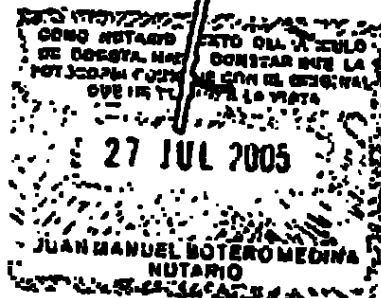
Legitimation

Por legajo notarial No. 2654/95.V

Fortifico la autenticidad de las firmas antecedentes puestas ante mí por los señores:

1. Dr. Dieter Landien, Dipl. Crim., domiciliado en 55127 Mainz,
2. Dr. Gerhard Huber, abogado, domiciliado en 55411 Bismun

a quienes conozco en persona.



igualmente certifico, por haber examinado en la fecha el registro de Comercio del Juzgado Municipal de Dingen, VR B 1063, que la firma Boehringer Ingelheim International GmbH, domiciliada en Ingelheim am Rhein, esta inscrita bajo el No. HK B 1063 en el Registro de Comercio del Juzgado Municipal de Dingen y que los señores Dr. Maunien y Dr. Huber, en su calidad de apoderados, estan facultados para representar conjuntamente a la sociedad.

Ingelheim am Rhein, 12 de diciembre de 1995/hin

Fdo.: firma ilegible

(Hilo / Hilo rojo en relieve.)

El notario suplente

El notario suplente - Ingelheim

del notario de Ingelheim

Prof. Dr. Weirich

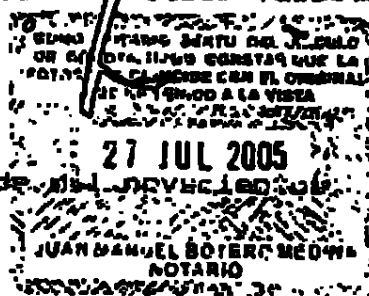
dos sellos redondos en tinta del Tribunal Regional de Mainz

Exo E 1

Se certifica la autenticidad de la firma anteriormente del Dr. Peter Wirth, como notario suplente del Prof. Dr. Weirich, notario de Ingelheim, y la del sello oficial que le acompaña. Igualmente se certifica que el mencionado notario estaba facultado para realizar ese acto oficial.

Mainz, trece de diciembre de 1995

noventa y cinco



9

El Presidente del Tribunal Regional

(2) Fdo.: firma ilegible

(Dr. Hanna Paul Luttentberg)

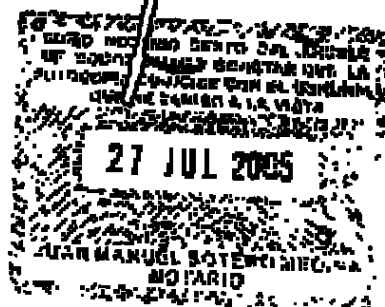
Costas

Derechos de legalización
(Valor: DM 3.000,-)
Decreto del 26 de Julio 1957
Gaceta Oficial 1 Pag. 961
DM 20,--
Mainz, 13 de diciembre de 1995
Fdo.: firma ilegible
Inspector

EN ESPAÑOL: La legalización de las firmas antecedentes por el
Consulado de Colombia en Munich bajo el No. 134 del 10 de
diciembre de 1995, y por el Ministerio de Relaciones Exteriores
de Colombia bajo el No. 051406 del 4 de enero de 1996.
Pagados derechos y Fondo Rotatorio US\$ 106,--

ES TRADUCCION FIEL Y COMPLETA, de la cual se dejó copia en los
archivos de estas oficinas para su confrontación.

Santafé de Bogotá, 6 de enero de 1996.

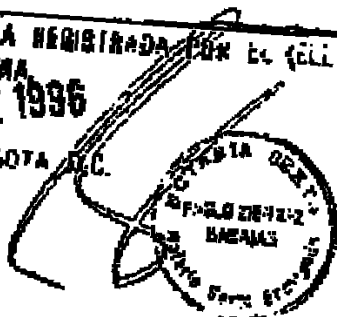


COMO NOTARIO SEXTO ENCARGADO DE SANTAFE
DE BOGOTA, HAGO CONSTAR QUE LA FIRMA DE

C. C.
CONCORDA CON LA REGISTRADA POR EL (ELL.)
EN ESTA NOTAMIA.

09 ENE 1996

SANTAFE DE BOGOTA DEC



RESPONSE AND TEXT
NO SE ASINE

1496 EYE 10 A 11:33

JEFFREY D. GALT **TECHNICAL**
SANITARY ENGINEER

JUL 2006

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1. 2. 3. 4. 5. 6. 7. 8. 9. 10. 11. 12. 13. 14. 15. 16. 17. 18. 19. 20. 21. 22. 23. 24. 25. 26. 27. 28. 29. 30. 31. 32. 33. 34. 35. 36. 37. 38. 39. 40. 41. 42. 43. 44. 45. 46. 47. 48. 49. 50. 51. 52. 53. 54. 55. 56. 57. 58. 59. 60. 61. 62. 63. 64. 65. 66. 67. 68. 69. 70. 71. 72. 73. 74. 75. 76. 77. 78. 79. 80. 81. 82. 83. 84. 85. 86. 87. 88. 89. 90. 91. 92. 93. 94. 95. 96. 97. 98. 99. 100. 101. 102. 103. 104. 105. 106. 107. 108. 109. 110. 111. 112. 113. 114. 115. 116. 117. 118. 119. 120. 121. 122. 123. 124. 125. 126. 127. 128. 129. 130. 131. 132. 133. 134. 135. 136. 137. 138. 139. 140. 141. 142. 143. 144. 145. 146. 147. 148. 149. 150. 151. 152. 153. 154. 155. 156. 157. 158. 159. 160. 161. 162. 163. 164. 165. 166. 167. 168. 169. 170. 171. 172. 173. 174. 175. 176. 177. 178. 179. 180. 181. 182. 183. 184. 185. 186. 187. 188. 189. 190. 191. 192. 193. 194. 195. 196. 197. 198. 199. 200. 201. 202. 203. 204. 205. 206. 207. 208. 209. 210. 211. 212. 213. 214. 215. 216. 217. 218. 219. 220. 221. 222. 223. 224. 225. 226. 227. 228. 229. 230. 231. 232. 233. 234. 235. 236. 237. 238. 239. 240. 241. 242. 243. 244. 245. 246. 247. 248. 249. 250. 251. 252. 253. 254. 255. 256. 257. 258. 259. 260. 261. 262. 263. 264. 265. 266. 267. 268. 269. 270. 271. 272. 273. 274. 275. 276. 277. 278. 279. 280. 281. 282. 283. 284. 285. 286. 287. 288. 289. 290. 291. 292. 293. 294. 295. 296. 297. 298. 299. 300. 301. 302. 303. 304. 305. 306. 307. 308. 309. 310. 311. 312. 313. 314. 315. 316. 317. 318. 319. 320. 321. 322. 323. 324. 325. 326. 327. 328. 329. 330. 331. 332. 333. 334. 335. 336. 337. 338. 339. 340. 341. 342. 343. 344. 345. 346. 347. 348. 349. 350. 351. 352. 353. 354. 355. 356. 357. 358. 359. 360. 361. 362. 363. 364. 365. 366. 367. 368. 369. 370. 371. 372. 373. 374. 375. 376. 377. 378. 379. 380. 381. 382. 383. 384. 385. 386. 387. 388. 389. 390. 391. 392. 393. 394. 395. 396. 397. 398. 399. 400. 401. 402. 403. 404. 405. 406. 407. 408. 409. 410. 411. 412. 413. 414. 415. 416. 417. 418. 419. 420. 421. 422. 423. 424. 425. 426. 427. 428. 429. 430. 431. 432. 433. 434. 435. 436. 437. 438. 439. 440. 441. 442. 443. 444. 445. 446. 447. 448. 449. 450. 451. 452. 453. 454. 455. 456. 457. 458. 459. 460. 461. 462. 463. 464. 465. 466. 467. 468. 469. 470. 471. 472. 473. 474. 475. 476. 477. 478. 479. 480. 481. 482. 483. 484. 485. 486. 487. 488. 489. 490. 491. 492. 493. 494. 495. 496. 497. 498. 499. 500. 501. 502. 503. 504. 505. 506. 507. 508. 509. 510. 511. 512. 513. 514. 515. 516. 517. 518. 519. 520. 521. 522. 523. 524. 525. 526. 527. 528. 529. 530. 531. 532. 533. 534. 535. 536. 537. 538. 539. 540. 541. 542. 543. 544. 545. 546. 547. 548. 549. 550. 551. 552. 553. 554. 555. 556. 557. 558. 559. 560. 561. 562. 563. 564. 565. 566. 567. 568. 569. 570. 571. 572. 573. 574. 575. 576. 577. 578. 579. 580. 581. 582. 583. 584. 585. 586. 587. 588. 589. 590. 591. 592. 593. 594. 595. 596. 597. 598. 599. 600. 601. 602. 603. 604. 605. 606. 607. 608. 609. 610. 611. 612. 613. 614. 615. 616. 617. 618. 619. 620. 621. 622. 623. 624. 625. 626. 627. 628. 629. 630. 631. 632. 633. 634. 635. 636. 637. 638. 639. 640. 641. 642. 643. 644. 645. 646. 647. 648. 649. 650. 651. 652. 653. 654. 655. 656. 657. 658. 659. 660. 661. 662. 663. 664. 665. 666. 667. 668. 669. 670. 671. 672. 673. 674. 675. 676. 677. 678. 679. 680. 681. 682. 683. 684. 685. 686. 687. 688. 689. 690. 691. 692. 693. 694. 695. 696. 697. 698. 699. 700. 701. 702. 703. 704. 705. 706. 707. 708. 709. 710. 711. 712. 713. 714. 715. 716. 717. 718. 719. 720. 721. 722. 723. 724. 725. 726. 727. 728. 729. 730. 731. 732. 733. 734. 735. 736. 737. 738. 739. 740. 741. 742. 743. 744. 745. 746. 747. 748. 749. 750. 751. 752. 753. 754. 755. 756. 757. 758. 759. 760. 761. 762. 763. 764. 765. 766. 767. 768. 769. 770. 771. 772. 773. 774. 775. 776. 777. 778. 779. 780. 781. 782. 783. 784. 785. 786. 787. 788. 789. 790. 791. 792. 793. 794. 795. 796. 797. 798. 799. 800. 801. 802. 803. 804. 805. 806. 807. 808. 809. 810. 811. 812. 813. 814. 815. 816. 817. 818. 819. 820. 821. 822. 823. 824. 825. 826. 827. 828. 829. 830. 831. 832. 833. 834. 835. 836. 837. 838. 839. 840.

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12117487375 CAVE UC

CAVELIER

ABOGADOS

EDIFICIO SISKI
CARRERA 49, No. 77-35
BOGOTA 8, COLOMBIA

COPIES BY TELEFONICO MUNDIAL. CAVE
TELEFONO (57) 111 7198100
CALL IT CAVELEYES

Señor Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

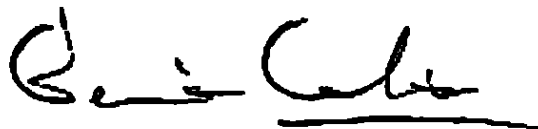
Poderdante: BOEHRINGER INGELHEIM INTERNATIONAL GMBH

Poder conferido el: 12-12-95.

Yo, GERMAN CAVELIER, obrando en mi calidad de apoderado principal del poderdante arriba mencionado atentamente manifiesto a Usted que sustituyo el poder que me ha sido conferido en la persona del doctor EMILIO FERRERO, Abogado con Tarjeta Profesional No. 31.929, con todas las facultades que me fueron conferidas.

Hago la anterior sustitución conforme al artículo 66 del Código de Procedimiento Civil ya que los otros sustitutos faltan en este momento.

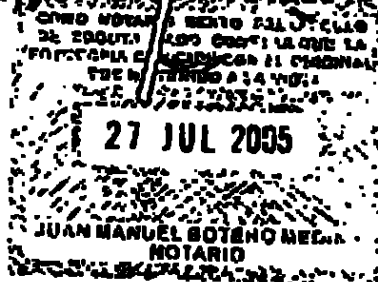
Señor Jefe,



GERMAN CAVELIER

T.P.A. No. 832

C.C. No. 2.817.921 de Bogotá



Acepto:



EMILIO FERRERO

T.P.A. No. 31.929

C.C. No. 438.019 de Usaquén

2e-780-2

NOTARIA SEXTA DE BOGOTÁ
RECONOCIMIENTO Y PRESENTACION PERSONAL

Bogotá, D. C. 11 FEB 1996

Ante M. PABLO XIENDEZ CARRILAS

NOTARIO SEXTO ENCARGADO DEL CIRCULO DE BOGOTÁ

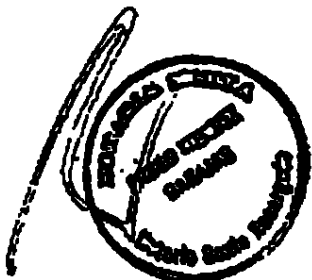
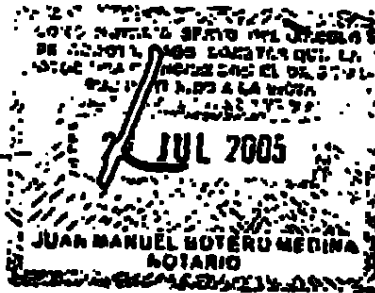
Comparación

quien(es) exhibió(n) el

y la(s) Libreta(s) de

domiciliada(s) en Bogotá y declaró(n) que la(s) firma(s) que
aparecen en el presente documento son la(s) suya(s) y
que el contenido del mismo es cierto.
En constancia se firma esta diligencia.

[Handwritten signature]



CAVELIER

ABOGADOS

EDIFICIO SISKI

CARRETERA No. 17-24
BOGOTÁ, D. C. - COLOMBIA

374

1-4445
Cave 10-228

ME-49

CESION

Yo, (nosotros) abajo firmante (s):

1. Anke ESFERESTER
2. Eckhard SCHAEFER
3. Fritz SACHER

Domiciliado(s)

en

1. Rosmerthstr. 84, 55126 Mainz, Alemania
2. Richard-Wimmer-Str. 23, 63150 Heusenstamm, Alemania
3. Kaiser-Karl-Str. 27, 55435 Gau-Algesheim, Alemania

Declaro/amos bajo juramento ser único(s) y verdadero(s)
titular(es) de la invención:

declaro/amos así mismo que cede/amos y transferimos, sin
limitación, a favor de la sociedad:

Boehringer Ingelheim International GmbH

constante y existente de conformidad con las leyes de

Alemania

domiciliada en Binger Strasse 173, 55216 Ingelheim,
Alemania

todos los derechos inherentes a dicha invención y que la citada
Compañía queda facultada para solicitar en su nombre la patente de
invención correspondiente en la República de Colombia.

ASSIGNMENT

I (we), the undersigned

1. Anke ESFERESTER
2. Eckhard SCHAEFER
3. Fritz SACHER

of

1. Rosmerthstr. 84, 55126 Mainz, Germany
2. Richard-Wimmer-Str. 23, 63150 Heusenstamm, Germany
3. Kaiser-Karl-Str. 27, 55435 Gau-Algesheim, Germany

state(s) under oath to be sole and true inventor(s) of the invention:
"Film coated tablet comprising an extract of red vine
leaves"

state as well, that assign, without reservations or limitations in favour
of Boehringer Ingelheim International GmbH

a corporation constituted and existing in conformity with the laws of
Germany

domiciled in Binger Strasse 173, 55216 Ingelheim,
Germany

all rights inherent to said invention and that the above mentioned
company hereby is enabled to apply, in its name, for the corresponding
patent invention, in the Republic of Colombia

Dado y firmado legítimamente y legal this

en

Firma/Signature

Anke ESFERESTER

Eckhard SCHAEFER

Fritz SACHER

© CAVELIER ABOGADOS
WPK19201-374

12

CERTIFICACIÓN NOTARIAL (INDIVIDUO)

A las _____ días del mes de _____
de 200 _____ Ante mí, Notario Público de _____

compareció(en) personalmente _____

a quien(es) doy fe de conocer y me consta que es(son) la(s)
persona(s) firmante(s) del documento que precede, y quien(es)
tiene(n) capacidad legal para otorgarlo

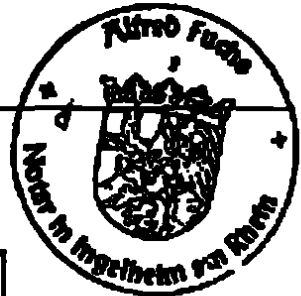
NOTARIO PÚBLICO-NOTARY PUBLIC

NOTARIAL CERTIFICATION (INDIVIDUAL)

On this 13th day of May
200 5 before me, a Notary ~~Public~~ of
Ingelheim am Rhein

personally appeared Mrs. Anke Espartero and
Mr. Eckhard Schäfer

to me known, and known to me to be the person(s) who executed
that foregoing document, and who have legal capacity to
execute it.



APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country:
This public document
2. has been signed by
3. acting in the capacity of
4. bears the seal/stamp of

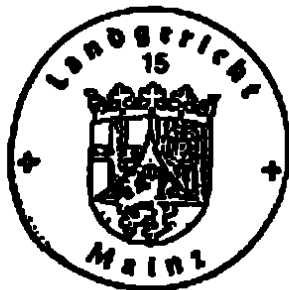
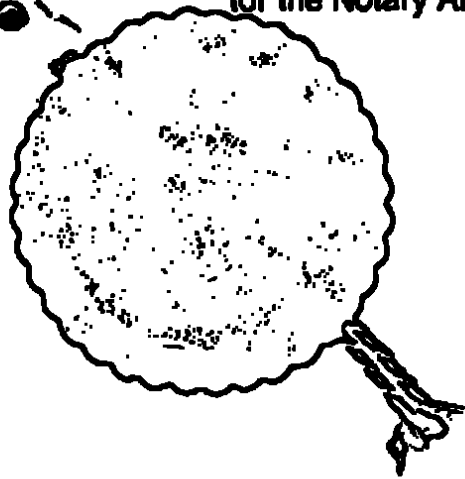
Certified

- | | |
|---------------|---------------|
| 5. at | 6. the |
| 7. by | |
| 8. No. | |
| 9. Seal/stamp | 10. Signature |

UR.Nr. 1139/2005

On this 1st day of June 2005 before me, a notary junior judge of the Notary Alfred Fuchs in Ingelheim am Rhein personally appeared Mr. Fritz Sacher to me known, and known to me to be the person who executed that foregoing document, and who has legal capacity to execute it.

Notary junior judge Daniela Seltenreich
Administrator of the Notary's Office
for the Notary Alfred Fuchs in Ingelheim



APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Land: Bundesrepublik Deutschland

Diese öffentliche Urkunde

2. ist unterschrieben von Notarassessorin Daniela Seltenreich
3. in seiner Eigenschaft als amtlich bestellte Vertreterin des Notars Alfred Fuchs in Ingelheim
4. sie ist versehen mit dem Dienststempel/Alfred Fuchs, Notar in Ingelheim am Rhein

Kostenrechnung:

Gebühr für die Erteilung
der Legalisation

Wert: 20.000,00 €

JVKostO v. 26.7.1957

i.V.m. § 45 KostO

Gebühr: 18,00 €

Mainz, 02.06.2005


Justizsekretärin z.A.

Bestätigt

5. In Mainz 6. am 02.06.05
7. durch den Präsidenten des Landgerichts
8. unter Nr. 689/05

9. Stempel/Siegel



10. Unterschrift


(Dr. Rolf Höfel)

14
TRADUCCIÓN OFICIAL No 07.18/05a realizada por Diego Vargas, Traductor
Oficial. Resolución No. 0001 de 1999 del Ministerio de Justicia y
registrado ante el Ministerio de Relaciones Exteriores de Colombia.

A continuación se traducen los sellos y legalizaciones de un
documento de Cesión escrito en inglés y español por medio del cual
1. Anke ESPEBESTER; 2. Eckhard SCHAEFER; 3. Fritz SACHER
domiciliados en 1. Rosmerthastr.84, 55126 Mainz, Alemania; 2.
Richard-Wimmer-Str.23, 63150 Heusenstamm, Alemania; 3. Kaiser-Karl-
Str.27, 55435 Gau-Algesheim, Alemania; respectivamente, declaran
bajo juramento ser únicos y verdaderos inventores de: "Comprinado
recubierto con película que comprende un extracto de hojas de parra
roja" y declaran así mismo que ceden y transfieren sin limitación a
favor de Boehringer Ingelheim International GmbH, una sociedad
constituida y existente de conformidad con las leyes de Alemania,
domiciliada en Binger Strasse 173, 55216 Ingelheim, Alemania, todos
los derechos inherentes a dicha invención y que la citada compañía
queda facultada para solicitar en su nombre la patente
correspondiente en la República de Colombia.

Firma Ilegible
Anke ESPEBESTER

Firma Ilegible
ECKHARD SCHAEFER

Firma Ilegible
Fritz SACHER

CERTIFICACIÓN NOTARIAL (INDIVIDUO) por medio de la cual se
certifican las firmas de la señora Anke Esperester y del señor
Eckhard Schäfer en el anterior documento así como su capacidad legal
para otorgarlo.

NOTARIO Firma Ilegible



(Anexo)

UR. Nr. 1139/2005

Hoy 1 de junio de 2005 ante mí, notario juez auxiliar de la Notaría Alfred Fuchs de Ingelheim am Rhein compareció personalmente el señor Fitz Saccher a quién conozco como la persona que suscribió el anterior documento y quién tiene la capacidad legal para otorgarlo.

Firma ilegible

Notario juez auxiliar Daniela Seltenreich

Administrador de la Oficina Notarial

en representación del Notario Alfred Fuchs de Ingelheim

Sello de Oblea

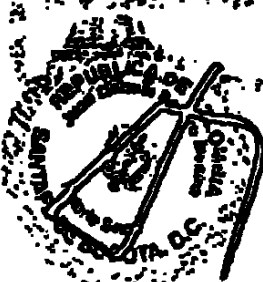
Sello de Apostille expedido en la República Federal de Alemania y certificada en Mainz el 02.06.05 con el Nr. 689/05 firmado por el Dr. Rolf Höfel.

Es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.

DVZ/ID-6923/WDCL002G/COLO 09253-841-024-4

Diego F. Vargas
DIEGO F. VARGAS Z.
TRADUCTOR E INTERPRETE OFICIAL
ESPAÑOL - INGLÉS - INGLÉS - ESPAÑOL
RES. 0001 DE ENERO 4 DE 1999
MINISTERIO DE JUSTICIA

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE
 BOGOTA, HAGO CONSTAR QUE LA(S) FIRMA(S) DE
Diego Felipe
Vargas
 CONCIDE(N) CON LA FIRMA REGISTRADA POR
 EL (S)ELLOS) EN ESTA NOTARIA
 SANTAFE DE BOGOTA, 19 JUL 2005



NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2005 JUL 19 A 11:53

LLOS
 OFICE DE LEGALIZACIONES
 SANTAFE DE BOGOTA D.C.

MINISTERIO DE RELACIONES
 EXTERIORES

134848

Diego Vargas
 CUYA FIRMA APARECE EN EL
 DOCUMENTO DESEMPLEA
 LAS FUERZAS ARMADAS

16

TRADUCCION OFICIAL No. 10857

de un documento escrito en Alemán, efectuada por Luz Arriaga de Herber, resolución del Ministerio de Justicia 599 del 6 de marzo 1978.-

Traducción de los sellos y autenticaciones en alemán que aparecen a continuación de un documento de Cesión, escrito en español e inglés, por medio del cual los señores

1. Anke ESPERESTER
2. Eckhard SCHAEFER
3. Fritz SACHER

domiciliado(s) en

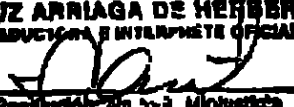
1. Rosmerthastr. 84, 55126 Mainz, Alemania
2. Richard-Wimmer-Str. 23, 63150 Heusenstamm, Alemania
3. Kaiser-Karl-Str. 27, 55435 Gau-Algesheim, Alemania

declaran bajo juramento ser únicos y verdaderos inventores de la invención

"Comprimido recubierto con una película que comprende un extracto de hojas de parra rojas"

y declaran así mismo que ceden y transfieren sin limitación a favor de la sociedad Boehringer Ingelheim International GmbH, constituida y existente de conformidad con las leyes de Alemania, domiciliada en Binger Strasse 173, 55216 Ingelheim, Alemania, todos los derechos inherentes a dicha invención y que la citada compañía queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia. Hay tres firmas ilegibles de los mencionados señores.

Certificación en inglés de las firmas antecedentes de los señores Esperester y Schäfer por el notario de Ingelheim am Rhein, Alfred Fuchs, el 13 de mayo 2005 bajo UR.No. 1023/2005 (sello redondo No. 2 en tinta).

LUZ ARRIAGA DE HERBER
TRADUCCION E INTERPRETE OFICIAL

Resolución No. 599 Ministerio de Justicia

17

(Sigue certificación en inglés de la firma del señor Sacher por la administradora de la notaría del notario Alfred Fuchs de Ingelheim, bajo UR 1139/2005 del 1 de junio 2005. – Hilo y olea notarial en relieve).

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. País: República Federal de Alemania

Este documento público

2. Ha sido firmado por Alfred Fuchs

3. Actuando en calidad de notario

4. Lleva el sello oficial del notario de Ingelheim am Rhein, Alfred Fuchs

Certificado

5. en Mainz

6. el 02.06.2005

7. por el Presidente del Tribunal Regional

8. bajo el No. 689/2005

9. Sello

Tribunal Regional de Mainz

(sello redondo No. 15)

10. Firma

Fdo.: ilegible

(Dr. Rolf Höfel)

Costes

Derechos de legalización

Valor: 20.000,00 €

JVKostO del 28.7.1957 en
combinación con Art. 45 KostO

Derechos: 18.00 €

Mainz, 02.06.2005

Fdo.: firma ilegible

Secretaría judicial z.A.

ES TRADUCCION FIEL Y COMPLETA, de la cual se deja copia en los archivos de estas
oficinas para su confrontación.

Bogotá, 15 de julio de 2005

C.2034

LUZ ARRIAGA DE HERBER -
TRADUCTORA INTERPRETE OFICIAL
Rafael Arriaga de Herber Mr. Sacher

COMO NOTARIO SEÑTO DEL CIRCULO DE SANTA F DE
BOGOTA, HAGO CONSTAR QUE LA(S) FIRMA(S) DE
Luz Beriega Heiber
CINQUESTA) CON LA FIRMA REGISTRADA POR
EL SELLOS) EN ESTA NOTARIA
SANTA F DE BOGOTA.
19 JUL 2005



NOT DE ASUADE
RESPONSABILIDAD DEL TEXTO

2005 JUL 19 A 11:53

Luz

JEFE DE LEGALIZACIONES
SANTA F DE BOGOTA B.C.

MINISTERIO DE RELACIONES
EXTERIORES

134846

Luz Amiggen
COTAFIRMA APARECE EN EL
DOCUMENTO DE SIEMPRE
LAS FUNCIONES INDICADAS

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
15 July 2004 (15.07.2004)

PCT

(11) International Publication Number
WO 2004/058227 A1

(51) International Patent Classification: A61K 9/28, 35/74

(21) International Application Number:
PCT/EP2003/014148

(22) International Filing Date:
12 December 2003 (12.12.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Date:
03030186.4 31 December 2002 (31.12.2002) EP
03019636.4 5 September 2003 (05.09.2003) EP

(71) Applicant (for all designated States except US):
WEITRINGER INGENIEUR-INTERNATIONAL
GMBH (DE/DE); Ringer Strasse 173, 55216 ENGLHEIM-
HEIM AM RHEIN (DE).

(72) Inventor(s):

(75) Inventor/Applicant (for US only): KSPENSTAL,
Anke (DE/DE); Koennerstrasse 84, 55126 MAINZ
(DE); SCHAEFER, Richard (DE/DE); Richard-Win-
ner-Strasse 23, 63199 HUNSrückTAMM (DE);
BACHER, Fritz (DE/DE); Kaiser-Karl-Straße 27,
55435 GAU-ALGERSHEIM (DE).

(74) Common Representative: INGENIEUR-INTERNATIONAL GMBH; Ringer Strasse 173,
55216 ENGLHEIM AM RHEIN (DE).

(81) Designated States (national): AE, AG, AI, AM, AT, AU,
AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR,
CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GR,
GU, GT, HN, HU, ID, IL, IN, JP, KE, KG, KP, KR,
KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN,
MW, MX, MY, NL, NO, NZ, OM, PG, PH, PL, PT, RO, RU,
SC, SD, SE, SG, SI, SJ, TH, TN, TR, TT, TZ, UA,
UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patents (BW, GH,
GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, EO, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FR, GB, GR, HU, IE, IT, LI, MC, NI, PT, RO, SI,
SK, TR), OAPI patents (BF, BJ, CN, CI, CM, GA,
GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— with international search report

For two-letter codes and other abbreviations, refer to the "Guidelines Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: FILM COATED TABLET COMPRISING AN EXTRACT OF RED VINE LEAVES

(57) Abstract: The invention relates to a film coated tablet comprising the following constituents: a) at least 50 % by weight of a dried extract of red vine leaves, which is obtainable by extraction of red vine leaves with water and drying; b) up to 50 % by weight of an excipient consisting essentially of at least one binder, at least one disintegrant, at least one filler, and a lubricant; and c) a matrix film consisting essentially of a film former, a plasticizer, a coating agent and optionally a coloring agent. Furthermore, the invention relates to an aqueous extract of red vine leaves is obtainable by a method comprising the steps of: a) collecting red vine leaves at a point of time when the content in flavonoids has reached an optimum; b) drying and crushing the leaves; c) cutting the leaves to pieces; d) extracting the leaves with water at elevated temperatures for 4 to 10 hours; e) concentrating and drying the obtained extract, and addition of up to 10 % by weight of a flow regulator during the relating to the final total amount of the resulting extract during the drying process (s).

WO 2004/058227 A1

FILM COATED TABLET COMPRISING AN EXTRACT OF RED VINE LEAVES

5 BACKGROUND OF THE INVENTION

1. TECHNICAL FIELD

The invention relates to a film coated tablet comprising a dried extract of red vine leaves, an excipient and a tablet film and the use thereof for the improvement of the blood circulation and/or the oxygen supply of the lower extremities.

10

2. BACKGROUND INFORMATION

Chronic venous insufficiency (CVI) is a progredient disease and will lead in many patients – especially if untreated – to oedema, coronal phlebectasia (Widmer stage I), hyperpigmentation, induration, lipodermatosclerosis, white atrophy (Widmer stage II), or varicose leg ulcers (Widmer stage III). Chronically disturbed haemodynamics of deep or superficial veins due to obstructed venous segments or valvular incompetence lead usually to skin diseases in the inner ankle area of the lower limbs.¹ Disturbances in the microcirculation of the skin have been considered to be major contributors for skin changes associated with chronic venous hypervolaemia and venous hypertension. (e.g. Fagrell B Vital microscopy and the pathophysiology of deep venous insufficiency. *Int Angiol* 1995;14:18-22.; Jünger M, Klysz T, Hahn M, Rasmann G. Disturbed blood flow regulation in venous leg ulcers. *Int J Microcirc* 1996;16:259-265).

Obviously, cutaneous microangiopathy of clinical relevance such as enlarged, tortuous capillaries surrounded by micro-oedema contributes to the skin alterations in the lower limbs and determines the course of CVI (Fagrell B, *loc. cit.* and Jünger M et al., *loc. cit.*).

The application of the laser Doppler technique in venous disorders is well illustrated. (e.g. Tulevski II, Ubbink DT, Jacobs MJHM. Red and green laser Doppler compared with capillary microscopy to assess skin microcirculation in the feet of healthy subjects. *Microvasc Res* 1999;58(2):83-88 and Bollinger A, Jäger K, Jünger M, Seifert H. The vascular laboratory: advances in non-invasive techniques. *World J Surg* 1988;12:724-731).

Different techniques have been developed to investigate microcirculation in both functionally different layers of the skin: the deeper, mainly thermoregulatory layer and the superficial, nutritive layer. Microcirculatory disturbances in the superficial nutritive layer are of utmost relevance for tropical skin changes. (Jünger M et al., *loc. cit.* and Gschwandtner ME, Ambrozy J, Pasching S, Willfort A, Schneider B, Bühler K, et al. Microcirculation in venous ulcers and surrounding skin: findings with capillary microscopy and laser Doppler imager. *Eur J Clin Invest* 1999;29:708-716).

The British patent GB 934,554 discloses that the capillary resistance of guinea pigs deficient in a vitamin can be enhanced by intraperitoneally administration of an alcoholic extract of vine leaves.

The International patent application WO 91/28363 discloses a method for preventing or alleviating the discomfort associated with mild-to-moderate chronic venous insufficiency of the lower extremities with the aid of an aqueous extract of red vine leaves. In addition a daily dosage regimen of 80 to 1000 mg divided up in 1 to 3 capsules is suggested.

The problem underlying the present invention was to provide a dosage form which allows to administer such high amounts of aqueous extract of red vine leaves in the suggested regimen. In view of patient compliance there is the requirement that such dosage forms shall not be too big, in order to facilitate swallowing. On the other hand the dosage form must have a high stability to ensure long shelf storage times. Moreover, high bioavailability is but a prerequisite for the therapeutic and/or preventive success of such a dosage form.

BRIEF SUMMARY OF THE INVENTION

It has been surprisingly found that a film coated tablet comprising:

- (a) at least 50 % by weight of a dried extract of red vine leaves, which is obtainable by extraction of red vine leaves with water and drying;
- (b) up to 50 % by weight of an excipient consisting essentially of
 - at least one binder,
 - at least one disintegrant,
 - at least one filler, and
 - a lubricant; and
- (c) a tablet film consisting essentially of a film former, a plasticizer, a coating agent and optionally a coloring agent;

fulfill these requirements and can be used to significantly enhance the microcirculation and the oxygen supply at the predominantly affected perimalleolar area of the leg in CVI patients.

Accordingly the invention relates to a film coated tablet comprising the following constituents:

- 5 (a) at least 50 % by weight of a dried extract of red vine leaves, which is obtainable by extraction of red vine leaves with water and drying;
- (b) up to 50 % by weight of an excipient consisting essentially of
- at least one binder,
 - at least one disintegrant,
 - 10 - at least one filler, and
 - a lubricant; and
- (c) a tablet film consisting essentially of a film former, a plasticizer, a coating agent and optionally a coloring agent.

15 Another aspect of the present invention is a process for preparing such a film coated tablet comprising the steps of:

- (A) mixing the dried aqueous extract of red vine leaves (a) with the excipients (b), optionally in the presence of a volatile diluent;
- (B) optionally screening the mixture obtained;
- 20 (C) compressing the mixture with a suitable tablet press; and
- (D) coating the resulting tablet with the tablet film (c).

Furthermore, the invention relates the use of such a film coated tablet for preparing a pharmaceutical or dietary composition for the treatment or prevention of the discomfort, disorder
25 and/or disease associated with chronic venous hypervolemia and venous hypertension.

Furthermore, the invention relates to an aqueous extract of red vine leaves, which is obtainable by a method comprising the steps of:

- (a) collecting red vine leaves at a point of time when the content in flavonoids has
30 reached an optimum;
- (b) drying and crushing the leaves;
- (c) cutting the leaves to pieces;
- (d) extracting the leaves with water at elevated temperatures for 6 to 10 hours;
- (e) concentrating and drying the obtained extract, and

- (f) addition of up to 10 % by weight of silica relating to the final total amount of the resulting extract.

5

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the schematic design of the clinical study which has been carried out to prove the efficacy of the film coated tablet according to the present invention.

Figure 2 shows the influence of the vine leaf extract containing film coated tablet

- 10 —○— AS195 360 mg compared with
—○— placebo

on the microcirculation measured with Laser Doppler flowmetry (LDF 10-37 kHz).

Figure 3 shows the influence of the vine leaf extract containing film coated tablet

- AS195 360 mg compared with
15 —○— placebo
on Transcutaneous oxygen partial pressure (tpO₂)

DETAILED DESCRIPTION OF THE INVENTION

20

The film coated tablet of the present invention consists of herbal ingredients derived by an aqueous extraction from red vine leaves (*folia vitis viniferae*; Extractum Vitis viniferae c folium spissum et siccum) and drying (a), excipients (b) and the tablet film (c). This extract contains flavon(ol)-glycosides, -glucuronides and flavonoids, with quercetin-3-O-β-D-glucuronide and isoquercitrin (quercetin-3-O-β-glucoside) as its main active ingredients. The range of their pharmacological actions has not yet been fully elucidated, but in-vitro studies indicate that they have antioxidant and anti-inflammatory properties and that they inhibit platelet aggregation and hyaluronidase and reduce oedema, possibly by reducing capillary permeability. Preclinical in-vivo experiments demonstrated anti-inflammatory and capillary wall thickening effects.

30

The film coated tablet according to the present invention comprises 50 to 70% of a dried aqueous red vine leaf extract with a high flavonoid content of 2-15%.

As a rule the relation by weight between the dried extract and the excipients used to produce the core of the tablet is between 1 : 1 to 2 : 1, preferably between 1.1 : 1 and 1.8 : 1, in particular between 1.25 : 1 and 1.75 : 1.

5 A film coated tablet comprising

- (a) 50 to 70 % by weight of said dried extract of red vine leaves;
- (b) 25 to 49 % by weight of said excipient, and
- (c) 1 to 5 % by weight of said tablet film,

based on the total mass of the film coated tablet, is preferred.

10

More preferred is a film coated tablet comprising

- (a) 51 to 59 %, in particular about 55 % by weight of said dried extract of red vine leaves;
- (b) 38 to 48 %, in particular about 43 % by weight of said excipient, and
- (c) 1 to 3 %, in particular about 2.7 % by weight of said tablet film,

15

based on the total mass of the film coated tablet.

Another preferred embodiment is a film coated tablet according, wherein the excipient (b) essentially consists of

20

- 70 to 85 % by weight of at least one binder,
- 0.5 to 12.5 % by weight of at least one disintegrant,
- 5 to 15 % by weight of at least one filler, and
- 1 to 5 % by weight of at least one lubricant,

based on the total mass of the combined excipients.

25

The term "binder" as used hereinbefore and hereinafter denotes an excipient which is suitable for binding other components to one another. Preferred binders according to the invention are selected from among:

- powdered cellulose, microcrystalline cellulose, sorbitol, starch, polyvinylpyrrolidone (povidone),
- 30 copolymers of vinylpyrrolidone with other vinyl derivatives (copovidone), cellulose derivatives, particularly methylhydroxypropylcellulose, e.g. Methocel A 15 LV, and mixtures of these compounds. The preferred binders are powdered cellulose, particularly microcrystalline cellulose and/or copovidone. If the abovementioned binders are used, the amount by weight, based on the total mass of the tablet according to the invention, is preferably in a range of 15 - 45 wt. %, more

preferably 25 - 40 wt.%, most preferably about 33 wt.%. Thanks to the particularly preferred binder microcrystalline cellulose, tablets are obtained having a high stability and good compliance for the patients to whom the aqueous extract of red vine leaves has to be administered.

5 The tablet according to the invention also contains disintegrants in addition to the abovementioned ingredients. Within the scope of the present invention these disintegrants may optionally also be known as breakdown agents. These are preferably selected, according to the invention, from among sodium starch glycolate, crosslinked polyvinylpyrrolidone (crospovidone), croscarmellose sodium salt (sodium salt of cellulose carboxymethyl ether, crosslinked), sodium-carboxymethylcellulose, dried maize starch, colloidal anhydrous silica and mixtures thereof. Within the scope of the present invention it is particularly preferred to use sodium starch glycolate, crospovidone and, preferably, the sodium salt of crospovidone or croscarmellose and colloidal anhydrous silica. Most preferred is a mixture of croscarmellose sodium, colloidal anhydrous silica and optionally crospovidone. If the abovementioned
10 disintegrants are used, the amount by weight, based on the total mass of the tablet according to the invention, is preferably in a range of about 0.5 - 10 wt.%, more preferably about 1.5 - 7.5 wt.%. Thanks to the particularly preferred combination of disintegrants, tablets are obtained having a high stability and provide high bioavailability to the aqueous extract of red vine leaves.

20 The tablet according to the invention also contains a filler. As a rule fillers are inert compounds such as inorganic metal oxides or inorganic phosphate or hydrogen phosphate. Preferably the filler is anhydrous calcium hydrogen phosphate. If the abovementioned fillers are used, the amount by weight, based on the total mass of the tablet according to the invention, is preferably
25 in a range of about 1 - 10 wt.%, more preferably about 2 - 8 wt.%.

The tablet according to the invention also contains flow agents or flow regulators and also lubricants, as additional ingredients. These include, within the scope of the present invention, ... - - for example, silicon dioxide, talc, stearic acid, sodium stearyl(fumarate, magnesium stearate and
30 glycerol tribeheate. According to the invention magnesium stearate is preferably used. If the abovementioned preferred lubricants are used, the amount by weight thereof, based on the total mass of the tablet according to the invention, is preferably in a range of about 0.1 - 10 wt.%, preferably about 0.5 - 5 wt.%, more preferably between 0.6 and 1.5 wt.%.

Furthermore preferred is a film coated tablet, wherein the tablet film (c) essentially consists of

- 50 to 85 % by weight of at least one film former,
- 5 to 10 % by weight of at least one plasticizer,
- 10 to 20 % by weight of at least one coating agent such as talc, and
- 5 - 0 to 15 % by weight of at least one colorant.

based on the total mass of the tablet film (c).

The tablet film according to the invention may also contain one or more synthetic or natural, pharmaceutically acceptable colorant, preferably one or more inorganic metal oxides such as
10 titanium dioxide (E 171) and/or ferric oxide (E 172). If the abovementioned preferred colorants are used the amount by weight thereof based on the total mass of the tablet according to the invention is 0.01 to 0.5 wt.%. .

It is a further object of the present invention to provide a film coated tablet for preventing and/or
15 alleviating the discomfort associated with mild-to-moderate chronic venous insufficiency of the lower extremities comprising herbal ingredients, wherein the tablet is manufactured pursuant to a controlled process that preserves the herbal curing qualities of the ingredients.

It is still a further object of the present invention to provide a film coated tablet which is
20 effective in preventing and/or alleviating the discomfort associated with mild-to-moderate chronic venous insufficiency of the lower extremities.

It is still a further object of the present invention to provide a film coated tablet for preventing and/or alleviating the discomfort associated with mild-to-moderate chronic venous insufficiency
25 of the lower extremities comprising herbal ingredients and having minimal or no side effects and thus being safe for internal consumption and a high stability and good patient compliance.

The aqueous extract prepared from dried red vine leaves is characterised by a high content of 2
to 20%, preferably 2 to 10 % of biologically active flavonoids.

30

The term "a person in need thereof" or "patient" as used hereinabove and hereinbelow relates to a female or male person who suffers from clinically not relevant early stages of chronic venous insufficiency (CVI) from proven CVI stage I and II according to Widmer. As a rule such patients are elderly people with an age of between 30 and 80, preferably between 32 and 76 years having

an mean age ($\pm$ standard deviation) of 55.2 ± 7.7 years. As a rule CVI is more expressed in female than in male patients.

In order that this invention be more fully understood, the following examples are set forth.

- 5 These examples are for the purpose of illustrating embodiments of this invention, and are not to be construed as limiting the scope of the invention in any way.

The examples which follow are illustrative and, as recognised by one skilled in the art, particular conditions could be modified as needed for individual compositions. Materials used in tests
10 below are either commercially available or easily prepared from commercially available materials by those skilled in the art.

The basis of the tablet is the aqueous extract of red vine leaves (*folias vitis viniferae* L.). The starting material for the preparation of the extract are red vine leaves collected at a point of time
15 where the content in flavonoids has reached an optimum. This is usually the case around the harvesting time of the grapes. The leaves are carefully dried and crushed. For extraction the leaves are cut to pieces of preferably 5 to 10 mm. To achieve a high content in flavonoids the extraction is done at elevated temperature, preferably at a temperature in the range of 60° to 80°C, over a time of at least 6 up to 10 hours. The preferred method is that of an exhaustive
20 percolation.

The so-called fluid extract obtained in the course of the extraction is concentrated by use of a suitable evaporator. The thick extract obtained in this step is dried, for instance by use of a vacuum drying oven or a vacuum drying conveyor.
25

All or some of the excipients may be added during drying to facilitate further processing of the extract. As a rule up to 10 % of one or more constituents of the excipients can be added during the drying process.

30 Preferably a part of the flow regulator such as colloidal, anhydrous silica is added to the extract during drying or before admixing with the other constituents. Preferably the resulting extract composition contains 0.5 to 10 % by weight, in particular 2.5 to 7.5 % by weight, most preferably about 4 % by weight of colloidal, anhydrous silica.

Surprisingly, tablets obtained from an extract to which a part of the excipients have been added during the drying process show an enhanced stability.

Most preferably the film coated tablet according to this invention consists of

- 5 ▪ 300 to 500 mg, preferably 320 to 400 mg, in particular about 355 to 380 mg of dry aqueous extract of red vine leaf (4-6 : 1) (*extractum vitis viniferae foliae aquosum siccum*), which may contain up to 10 % weight of a flow regulator, in particular colloidal, anhydrous silica;
- 10 ▪ the following excipients of the tablet core:
 - microcrystalline cellulose, croscarmellose sodium, calcium hydrogen phosphate (anhydrous), colloidal silica (anhydrous), magnesium stearate, and optionally crospovidone, and
- 15 ▪ a tablet film consisting of:
 - hypromellose, glyceryl tristearate, titanium dioxide (E 171), talc, ferric oxide, red (E 172).

Film coated tablets were prepared with the ingredients listed in the following tables A and B:

Table A

20

| Name of ingredient | Quantity per film coated tablet
[mg / 658.000 mg] | Function |
|--|--|--|
| <u>Tablet Core</u> | | |
| Vitis viniferae folium
dry extract aqueous
(4 - 6 : 1) | 360.000 | Active ingredient |
| Microcrystalline cellulose | 219.000 | Binder, disintegrant |
| Croscarmellose sodium | 18.000 | Disintegrant |
| Calcium hydrogen
phosphate, anhydrous | 30.000 | Filler |
| Silica, colloidal, anhydrous | 4.000 | Flow regulator,
disintegration
accelerator |

-10-

| | | |
|---------------------------|--------|-----------------|
| Magnesium stearate | 9.000 | Lubricant |
| Tablet Film | | |
| Hypromellose | 11.383 | Film former |
| Glyceryl tristearate | 1.138 | Plasticizer |
| Titanium dioxide (E 171) | 0.783 | Colouring agent |
| Talc | 3.131 | Coating agent |
| Ferric oxide, red (E 172) | 1.565 | Colouring agent |

The extract is mixed with the excipients of the tablet core and compressed on a suitable tablet press.

Table B

| Name of ingredient | Quantity per film coated tablet
[mg / 658.000 mg] | Function |
|--|--|--|
| <u>Tablet Core</u> | | |
| <i>Vitis vinifera</i> folium
dry extract aqueous
(4 - 6 : 1) | 360.000 | Active ingredient |
| Silica, colloidal, anhydrous | 15.000 | binder |
| Microcrystalline cellulose | 214.000 | Binder, disintegrant |
| Croscarmellose sodium | 18.000 | Disintegrant |
| Calcium hydrogen
phosphate, anhydrous | 30.000 | Filler |
| Silica, colloidal, anhydrous | 6.000 | Flow regulator,
disintegration
accelerator |
| Magnesium stearate | 9.000 | Lubricant |
| Crospovidone | 18.000 | Disintegrant |
| <u>Tablet Film</u> | | |
| Hypromellose | 11.383 | Film former |
| Glyceryl triacetate | 1.138 | Plasticizer |
| Titanium dioxide (E 171) | 0.783 | Colouring agent |
| Talc | 3.131 | Coating agent |
| Ferric oxide, red (E 172) | 1.565 | Colouring agent |

The extract is mixed with 15,000 mg silica during the drying process, which yields an extract
 5 consisting of 96 % by weight of the ingredients of the extract and 4 % of silica. This resulting
 mixture is mixed with the remaining excipients of the tablet core and compressed on a suitable
 tablet press.

The compression forces which are needed to produce tablets of suitable breaking resistance and
 10 hence with the required breakdown times are dependent on the shapes and sizes of the punching
 tools used. Compression forces in the range from 2 - 20 kN are preferred. Higher compression

forces may lead to tablets with a delayed released of active substance. Lower compression forces may produce mechanically unstable tablets. The tablet cores may have different shapes; the preferred shapes are round biplanar or biconvex and oval or oblong forms.

- 5 The coating solution is prepared by mixing the film-forming agent with the colouring materials and a plasticizer in water. Using a suitable coating pan the film-coating solution is applied on to the tablet cores.

10 Preferably the tablets have an oblong shape to facilitate swallowing. In the case of a film-coated tablet containing 360 mg of extract and an extract to excipient ratio as indicated before, an oblong tablet may be about 17-18 mm long and have a width of about 8 to 9 mm. These film coated tablets of Table A are hereinbelow coded "AS 19T".

15 To enhance the blood circulation and/or the oxygen supply of the lower extremities, the tablet should be taken in dosages corresponding to 150 and 1000 mg of extract, preferably 300-800 mg, in particular 350-750 mg daily. The total amount of extract may be divided up in 1 to 3 film coated tablets a day. The daily dose should be taken at once, preferably in the morning.

Impressive improvement of the symptoms can be expected within 6 weeks of continuous use.
20 The optimum effect is maintained or amplified on longer use.

Methods

Participants

- 25 Male and female patients, age 18 years or more, with proven CVI I or CVI according to Widmer, with diagnosis confirmed and present for at least one year were enrolled. Medically relevant concomitant diseases have to be absent. Patients who used drugs to alleviate their CVI symptoms within 4 weeks or were treated with theophyllin, diuretics, cardiac glycosides, ACE inhibitors or calcium antagonists within 8 days prior to the first examination were not allowed to be enrolled.
30 Compression bandages or concomitant therapy for venous problems were forbidden during the participation in the trial.

Design and procedures

The double-blind, randomised, placebo-controlled cross-over trial was run according to the principles of the declaration of Helsinki and the International Conference of Harmonisation of Good Clinical Practice.

5

Each patient participated for 17 weeks in the trial: for a one-week wash-out (placebo-treated), for a 6-week treatment period (Group_1 starting with AS 195, Group_2 starting with placebo), for a 4-week wash-out (placebo-treated), and for a second 6-week treatment period (Group_1 continuing with placebo, Group_2 continuing with the).

10

AS 195 (film-coated tablets containing 360 mg dry extract of red vine leaves) or placebo tablets were taken according to the randomisation schedule as single dose in the morning. Both tablets were identical with respect to size, shape, weight, inner appearance, and taste.

For laser Doppler flowmetry the equipment was provided by LMTB, Berlin, Germany (e.g. Doerschel K, Mueller G. Velocity resolved laser Doppler flow measurement in skin.

15

Lasermedizin 1996;12:163-171.). The equipment is a computer-based mobile unit using a laser frequency of 785 nm. The laser probe was fixed 3.5 cm distal to the inner ankle of the more affected leg. After 30 minutes sitting for adaptation to room temperature, measurement started after 10 minutes standing (256 points of measurement, duration of measurement: approx. 0.4 seconds). The back-scattered light was retrieved by two diodes in the range of frequencies

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between 0.2 to 37.2 kHz. The data were processed using a Fast Fourier Transformation. Finally, the output referred to the range of frequencies between 0.2 to 10.0 kHz for vessels in the reticular venous plexus (larger mainly thermoregulative vessels, diameter more than 30 micrometer) and to the range of frequencies between 10.1 to 37.2 kHz for capillaries in the subpapillary venous plexus (superficial small nutritive vessels, diameter 6 to 30 micrometer).

25

Transcutaneous oxygen pressure (tcPO₂) was measured using modified Clark-type polarographic electrodes containing noble metal cathodes and silver/silver chloride anodes (TCM 3, Radiometer Copenhagen, Brønshøj, Denmark). A heating element adjacent to the anode maintained skin temperature at 43° Celsius. At this temperature the arterioles are maximally dilated, tcPO₂ approximates the PO₂ of arterial blood (e.g. Bollinger A, Jäger K, Jünger M, Seifert H. The vascular laboratory: advances in non-invasive techniques. World J Surg 1988;12:724-731.).

30

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The electrode was attached to the skin surface by an adhesive ring device which was filled with physiological saline, 3.5 cm antrolateral from the Laser Doppler probe. After 30 minutes sitting for adaptation to room temperature, measurement started after 10 minutes of standing. A measurement lasted approx. 15 minutes. The $tcPO_2$ values are expressed in millimeter mercury column (mmHg). Normal values available for the dorsum of the foot of patients without CVI are

5 ranged between 40 and 80 mmHg.

Local skin temperature was measured with a thermistor fixed adjacent to the oxygen electrode in the perimalleolar region. In order to minimise effects on the skin perfusion, LDF and $tcPO_2$

10 measurements were conducted between 28 and 32° C local skin temperature.

Calf and ankle circumference were measured using a measuring tape. Measurements were carried out at the lateral and medial ankle and at the middle of the calf.

15 Subjective symptoms of CVI (tired heavy legs, sensation of tension, tingling sensation, and pain) were measured by using a 10-cm visual analogue scale with zero as "none at all" and 10 cm as "very strong".

Overall treatment efficacy was rated by patients and investigators on a 4-point verbal rating scale (good, satisfactory, not satisfactory, and bad) at the end of each treatment period.

20

Overall tolerability was rated by patients and investigators on a 4-point verbal rating scale (good, satisfactory, not satisfactory, and bad). The patients were questioned about their well-being in general terms at each visit.

25

Results

Seventy-one women and men aged between 32 and 76 years with proven CVI stage I and II according to Widmar were included. The mean age ($\pm$ standard deviation) was 55.2 ± 7.7 years; 55 were women, 16 men. The phlebological status revealed moderate or severe intensity of

30 varicosis in 47 (67.1%), pigmentation in 27 (38.6%), ankle oedema in 26 (37.1%), and lower leg oedema in 25 (35.7%) patients. Mild signs of atrophy were present in 13 patients (18.6%), of eczema in none (Table 1).

Table 1: Demographics and baseline characteristics of CVI

| | AS 195 / Placebo
(n=36) | Placebo / AS195
(n=35) |
|--|----------------------------|---------------------------|
| Continuous variates (median (range)) | | |
| Age [years] | 66 (32-76) | 66 (37-76) |
| Height [cm] | 168 (150-186) | 165 (150-191) |
| Weight [kg] | 76.5 (48-97) | 73 (55-120) |
| Body mass index [kg/m ²] | 27.6 (20.6-32.0) | 26.7 (20.1-42.5) |
| Systolic blood pressure [mmHg] | 130 (100-150) | 135 (120-140) |
| Diastolic blood pressure [mmHg] | 80 (60-90) | 80 (65-90) |
| Categorical variates (n (%)) | | |
| Female | 24 (66.7) | 31 (88.6) |
| Current smoker | 4 (11.1) | 1 (2.9) |
| CVI stage | | |
| Stage I | 26 (72.2) | 23 (65.7) |
| Stage II | 10 (27.8) | 12 (34.3) |
| Phlebological status of moderate to severe intensity | | |
| Varicosis | 26 (72.2) | 22 (62.9) |
| Pigmentation | 11 (30.6) | 17 (48.6) |
| Atrophy | 0 (0.0) | 0 (0.0) |
| Eczema | 0 (0.0) | 0 (0.0) |
| Ankle oedema | 13 (36.1) | 14 (40.0) |
| Lower leg oedema | 12 (33.3) | 14 (40.0) |

- 5 Protocol violations did not occur in the remaining patients. Therefore, all patients remained in the intention to treat analyses (Figure 1). Patient characteristics were homogenously distributed across the two treatment sequences (Group_1, Group_2) except for the sex ratio (12 men in Group_1, 4 men in Group_2) (Table 1). Baseline values for the laser Doppler parameters, transcutaneous oximetry, ankle and calf circumferences, and subjective symptoms were
- 10 comparable for Group_1 and Group_2 (Table 2). Compliance with the film coated tablet according to the invention was approximately 100% in both treatment sequences.

Table 2: Mean ($\pm$ SD) of baseline characteristics of each treatment period

| | Period 1 | | Period 2 | |
|---------------------------------------|------------------|-------------------|------------------|-------------------|
| | AS 195
(n=36) | Placebo
(n=34) | AS 195
(n=34) | Placebo
(n=36) |
| Laser Doppler Flowmetry [AU] | | | | |
| 10-37 kHz | 303.5 (135.2) | 333.5 (153.0) | 275.4 (126.4) | 293.3 (119.9) |
| < 10 kHz | 352.7 (87.7) | 370.8 (120.0) | 174.7 (77.0) | 189.4 (67.6) |
| Transcutaneous Oximetry [mmHg] | | | | |
| | 32.1 (7.0) | 32.3 (6.4) | 30.1 (6.2) | 30.8 (6.4) |

| | | | | |
|---------------------------------|------------|------------|------------|------------|
| Circumference [cm] | | | | |
| Ankle | 20.3 (2.2) | 20.4 (2.4) | 20.2 (2.6) | 20.3 (2.2) |
| Calf | 34.7 (3.1) | 34.2 (3.0) | 34.0 (3.1) | 34.6 (3.2) |
| Subjective symptoms [cm] | | | | |
| Tired/heavy legs | 4.3 (2.8) | 3.7 (2.9) | 4.6 (2.9) | 5.2 (2.6) |
| Pain in legs | 4.0 (3.2) | 3.2 (3.1) | 4.5 (2.7) | 4.9 (3.1) |
| Sensation of tension | 4.5 (2.9) | 4.1 (2.8) | 4.5 (2.6) | 5.1 (2.5) |
| Tingling sensation | 3.3 (3.1) | 2.7 (2.9) | 3.7 (2.6) | 4.2 (2.8) |

Laser Doppler Flow measurements in the frequency range of 10-37 kHz were elected for the primary endpoint. These frequencies are considered to be determined by the number of erythrocytes and their movements (flow velocity) in the capillaries of the superficial layer of the skin of the leg. After 6 weeks the laser Doppler frequencies (10-37 kHz) increased in the AS 195 group (plus 241.8±18.7 AU) but decreased in the placebo group (minus 41.0±18.7 AU, p<0.0001) (Table 3). This effect was present as early as 3 weeks after start of treatment (p<0.0001) (Table 4, Figure 2).

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Table 3: Mean ($\pm$ SEM) of change from baseline adjusted for period effects, 95 % confidence interval for treatment contrasts and p value after 3 weeks treatment with 360 mg AS 195 or placebo

| | Treatment | | Difference
(n=70) | Treatment contrast | |
|--------------------------|------------------|-------------------|----------------------|-------------------------------|----------|
| | AS 195
(n=70) | Placebo
(n=70) | | Confidence interval
(n=70) | p value |
| Week 3 | | | | | |
| Laser Doppler Flowmetry | | | | | |
| [AU] | | | | | |
| 10-37 kHz | 132.2 (11.9) | -28.2 (11.9) | 160.5 | 127.0 to 194.0 | < 0.0001 |
| < 10 kHz | -3.7 (9.2) | -99.9 (9.2) | 96.2 | 70.2 to 122.2 | < 0.0001 |
| Transcutaneous Oximetry | | | | | |
| | 0.62 (0.97) | -3.84 (0.97) | 4.46 | 1.72 to 7.20 | 0.0018 |
| [mmHg] | | | | | |
| Circumference [cm] | | | | | |
| Ankle | -0.19 (0.09) | 0.21 (0.09) | -0.40 | -0.65 to -0.15 | 0.0025 |
| Calf | -0.24 (0.04) | 0.04 (0.04) | -0.28 | -0.40 to -0.17 | < 0.0001 |
| Subjective symptoms [cm] | | | | | |
| Tired/heavy legs | -0.94 (0.25) | 0.21 (0.25) | -0.73 | -1.42 to -0.04 | 0.0396 |
| Pain in legs | -1.17 (0.23) | -0.24 (0.23) | -0.94 | -1.59 to -0.28 | 0.0061 |
| Sensation of tension | -1.00 (0.24) | -0.52 (0.24) | -0.49 | -1.17 to 0.19 | 0.1588 |
| Tingling sensation | -0.99 (0.26) | -0.20 (0.26) | -0.79 | -1.52 to -0.06 | 0.0335 |

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Table 4: Mean ($\pm$ SEM) of change from baseline adjusted for period effects, 95 % confidence interval for treatment contrasts and p value after 6 weeks treatment with 360 mg AS 195 or placebo

| | Treatment | | Difference
(n=70) | Treatment contrast | | p value |
|--------------------------------|------------------|-------------------|----------------------|-------------------------------|--|----------|
| | AS 195
(n=70) | Placebo
(n=70) | | Confidence interval
(n=70) | | |
| Week 6 | | | | | | |
| Laser Doppler Flowmetry [AU] | | | | | | |
| 10-37 kHz (primary endpoint) | 241.8 (18.7) | 41.0 (18.7) | 282.8 | 229.9 to 335.7 | | < 0.0001 |
| < 10 kHz | 57.0 (12.4) | -107.7 (12.4) | 164.7 | 129.7 to 199.7 | | < 0.0001 |
| Transcutaneous Oximetry [mmHg] | | | | | | |
| Circumference [cm] | 1.35 (0.97) | -7.27 (0.97) | 8.63 | 5.88 to 11.38 | | < 0.0001 |
| Ankle | -0.39 (0.09) | 0.29 (0.09) | -0.68 | -0.94 to -0.43 | | < 0.0001 |
| Calf | -0.54 (0.05) | 0.14 (0.05) | -0.68 | -0.83 to -0.53 | | < 0.0001 |
| Subjective symptoms [cm] | | | | | | |
| Tired/heavy legs | -0.78 (0.33) | -0.94 (0.33) | 0.16 | -0.76 to 1.09 | | 0.7285 |
| Pain in legs | -0.76 (0.35) | -0.86 (0.35) | 0.10 | -0.88 to 1.09 | | 0.8323 |
| Sensation of tension | -0.96 (0.35) | -1.40 (0.35) | 0.44 | -0.46 to 1.44 | | 0.3819 |
| Tingling sensation | -0.55 (0.30) | -0.66 (0.30) | 0.11 | -0.75 to 0.96 | | 0.8044 |

Laser Doppler Flow measurements in the frequency range below 10 kHz are considered to be determined by the number of erythrocytes and their movements (flow velocity) in the capillaries in the deeper mainly thermoregulative layer of the skin of the leg. After 6 weeks the laser Doppler frequencies below 10 kHz) increased in the AS 195 group (plus
5 57.0 ± 12.4 AU) and decreased in the placebo group (minus 107.7 ± 12.4 AU, $p < 0.0001$) (Table 3). This effect seems to depend on the climatic condition during the treatment period. During the study period of moderate temperatures (April/May) the Laser Doppler measurements (< 10 kHz) remained unchanged in the AS 195 treatment group after an initial drop whereas the measurements in the placebo group decreased ($p < 0.0001$). During
10 the study period of higher temperatures (July/August) the laser Doppler measurements (< 10 kHz) increased in the AS 195 treatment group and remained constant in the placebo group. ($p < 0.0001$).

The transcutaneous oxygen pressure increased in the AS 195 group (plus 1.35 ± 0.97
15 mmHg) but decreased in the placebo group (minus 7.27 ± 0.97 mmHg, $p < 0.0001$). This observation was consistent in both treatment periods and would therefore be in line with the Laser Doppler Flow in the nutritive superficial layer of the skin (i.e., 10-37 kHz) (Table 3.4, Figure 3).

20 The statistically significant and clinically relevant reduction of ankle (after 3 weeks: AS 195 minus 0.19 ± 0.09 cm, placebo plus 0.21 ± 0.09 cm, $p = 0.0025$) and calf circumferences (after 3 weeks: AS 195 minus 0.24 ± 0.04 cm, placebo plus 0.04 ± 0.04 cm, $p < 0.0001$) indicate an onset of action as early as 3 weeks after start of treatment (Table 3). This effect becomes more pronounced after 6 weeks (AS 195 ankle: minus 0.39 ± 0.09 cm,
25 calf: minus 0.54 ± 0.05 ; placebo ankle: plus 0.29 ± 0.09 cm, calf: plus 0.14 ± 0.05 cm, $p < 0.0001$) (Table 4)

There was no relevant change of the intensity of the subjective symptoms related to CVI
after 6 weeks of treatment. This result is in line with those of a previous study where
30 subjective symptoms measured on a visual analogue scale were reduced only after longer treatment periods (12 weeks).

- 20 -

Adverse events occurred rarely in this study. Thirteen of 71 patients experienced at least one adverse event, 12 of them experienced the onset of action while on placebo treatment, one while on AS 195 (bronchitis, moderate intensity, considered not drug related by the investigator). The patient who died from cardiac arrest had been treated with placebo
5 (never received AS 195 in this trial). All patients assessed the overall tolerability as good or satisfactory. The laboratory parameters did not change during the study.

Discussion

It has been shown in a previous study (WO 01/28363) that red vine leaves extract AS 195
10 reduces lower leg oedema, calf circumference, and ankle circumference in addition to improving subjective symptoms related to chronic venous insufficiency in patients treated once daily for 12 weeks.⁷ The present study was designed to provide additional information on the underlying mechanism of action by investigating microcirculation as a clinically relevant surrogate parameter for CVI related leg problems. This study is the first
15 one in CVI patients aimed to investigate in addition to leg oedema reduction further clinical relevant effects related to the therapy with red vine leaves extract. The reduced venous drainage results in impaired cutaneous microcirculation with trophical disturbances of the skin. If CVI remains untreated this condition may even result venous leg ulcers. Laser Doppler flowmetry, as used in the present study, is a valid and sensitive method to
20 measure objective treatment effects which may be related to the subjectively experienced volume reduction after 3 months of treatment.

The study results fit into the clinical data available for AS 195 and add information on the onset of action. The leg volume as an objective parameter will be reduced in a clinically
25 relevant and statistically significant degree after 6 weeks of treatment. This objective effect has also been reported recently with horse chestnut seed extract (e.g. Diehm C, Trampisch HJ, Lange S, Schmidt C. Comparison of leg compression stocking and oral horse-chestnut seed extract therapy in patients with chronic venous insufficiency. Lancet 1996;347:292-294.) and Butcher's Broom (e.g. Vanscheidt W, Jost V, Wolna P, et al. Efficacy and safety
30 of a Butcher's Broom preparation (Ruscus aculeatus L. extract) compared to placebo in patients suffering from chronic venous insufficiency. Drug Res 2002;52(4):243-250.).

In the present study it was shown that the laser Doppler flowmetry parameters, the ankle and calf circumferences and the transcutaneous oxygen pressure were affected as early as after 3 weeks of treatment. In contrast, the subjective symptoms of CVI rated on a visual analogue scale were not significantly different from placebo after 6 weeks of treatment as they were in the previous study. A treatment duration of 12 weeks is mandatory for a relevant reduction of subjective CVI symptoms.

The present results suggest a major role of red vine leaves extract in prevention of CVI progression and the occurrence of trophical skin lesions and may even prevent or delay the transition from clinically not relevant early stages of CVI to CVI Stage I.

+6
HC**CLAIMS:**

1. A film coated tablet comprising the following constituents:
- (a) at least 50 % by weight of a dried extract of red vine leaves, which is obtainable by extraction of red vine leaves with water, drying and optionally addition of up to 10 % by weight of silica relating to the total amount of component (a);
- (b) up to 50 % by weight of an excipient consisting essentially of
- at least one binder,
 - at least one disintegrant,
 - at least one filler, and
 - a lubricant; and
- (c) a tablet film consisting essentially of a film former, a plastiziser, a coating agent and optionally a coloring agent.
2. A film coated tablet according to claim 1 comprising
- (a) 50 to 70 % by weight of said dried extract of red vine leaves;
- (b) 25 to 49 % by weight of said excipient, and
- (c) 1 to 5 % by weight of said tablet film,
- based on the total mass of the film coated tablet.
3. A film coated tablet according to claim 1 or 2 comprising
- (a) 51 to 59 % by weight of said dried extract of red vine leaves;
- (b) 38 to 48 % by weight of said excipient, and
- (c) 1 to 3 % by weight of said tablet film,
- based on the total mass of the film coated tablet.

4. A film coated tablet according to any of the preceding claims, wherein the aqueous extract of red vine leaves is obtainable by a method comprising the steps of:

- (a) collecting red vine leaves at a point of time when the content in flavonoids has reached an optimum;
- 5 (b) drying and crushing the leaves;
- (c) cutting the leaves to pieces;
- (d) extracting the leaves with water at elevated temperatures for 6 to 10 hours;
- (e) concentrating and drying the obtained extract, and
- 10 (f) and optionally addition of up to 10 % by weight of flow regulator relating to the final total amount of the resulting extract during the drying process (e).

5. A method according to claim 4 wherein the leaves in step (iv) are extracted with water at temperatures from 60 to 80 °C.

15

6. A film coated tablet according to any of the preceding claims, wherein the excipient (b) essentially consists of

- 70 to 85 % by weight of at least one binder,
- 20 - 0,5 to 12,5 % by weight of at least one disintegrant,
- 5 to 15 % by weight of at least one filler, and
- 1 to 5 % by weight of at least one lubricant,

based on the total mass of the excipients (b).

25

7. A film coated tablet according to any of the preceding claims, wherein the binder is selected from among powdered cellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone, copolymers of vinylpyrrolidone with other vinyl derivatives, cellulose derivatives and mixtures of these compounds.

30

8. A film coated tablet according to any of the preceding claims, wherein the disintegrant is selected from among colloidal silica, sodium starch glycolate, crosslinked polyvinylpyrrolidone (crospovidone), croscarmellose sodium salt (sodium salt of cellulose carboxymethyl ether, crosslinked), sodium-carboxymethylcellulose, dried maize starch and
5 mixtures thereof.

9. A film coated tablet according to any of the preceding claims, wherein the filler is an inorganic phosphate or hydrogen phosphate.
10

10. A film coated tablet according to any of the preceding claims, wherein the filler is selected among from silicon dioxide, talc, stearic acid, sodium stearyl fumarate, magnesium stearate and glycerol tribehenate.
15

11. A film coated tablet according to any of the preceding claims, wherein the tablet film (c) essentially consists of
- 50 to 85 % by weight of at least one film former,
20 - 5 to 10 % by weight of at least one plasticizer,
- 10 to 20 % by weight of at least one coating agent, and
- 0 to 15 % by weight of at least one colorant.
based on the total mass of the tablet film (c).

25 12. Process for preparing a film coated tablet according to one of claims 1 to 11 comprising the steps of:

- (A) mixing the dried aqueous extract of red vine leaves (a) with the excipients (b), optionally in the presence of a volatile diluent;
30 (B) optionally screening the mixture obtained;
(C) compressing the mixture with a suitable tablet press; and

- 25 -

(D) coating the resulting tablet with the tablet film (c).

13. Use of a film coated tablet according to one of claims 1 to 11 for preparing
5 a pharmaceutical or dietary composition for the treatment or prevention of the discomfort,
disorder and/or disease associated with chronic venous hypervolaemia and venous
hypertension.

10 14. An aqueous extract of red vine leaves is obtainable by a method comprising
the steps of:

- (a) collecting red vine leaves at a point of time when the content in flavonoids has
reached an optimum;
- (b) drying and crushing the leaves;
- 15 (c) cutting the leaves to pieces;
- (d) extracting the leaves with water at elevated temperatures for 6 to 10 hours;
- (e) concentrating and drying the obtained extract, and
- (f) addition of up to 10 % by weight of a flow regulator during the relating to the final
total amount of the resulting extract during the drying process (e).

20

15. The aqueous extract according to claim 14, which comprises 2.5 to 7.5 % by
weight of colloidal, anhydrous silica.

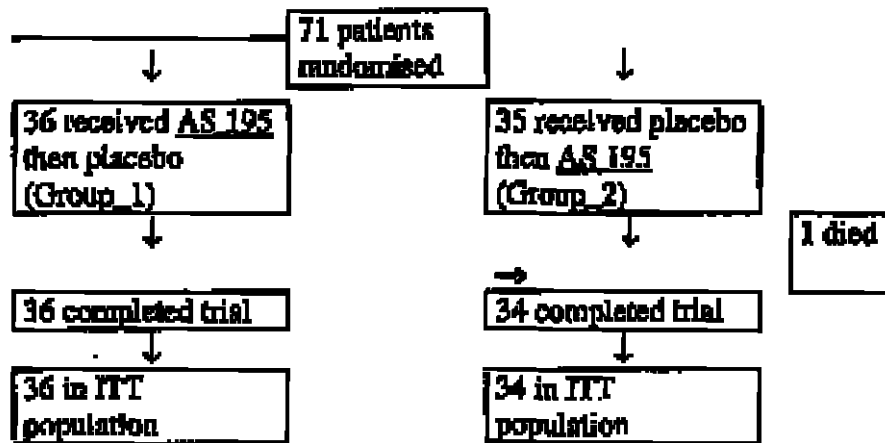
25 16. The aqueous extract according to claim 15, which comprises about 4.0 % by
weight of colloidal, anhydrous silica.

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DRAWINGS

5



10

Fig. 1

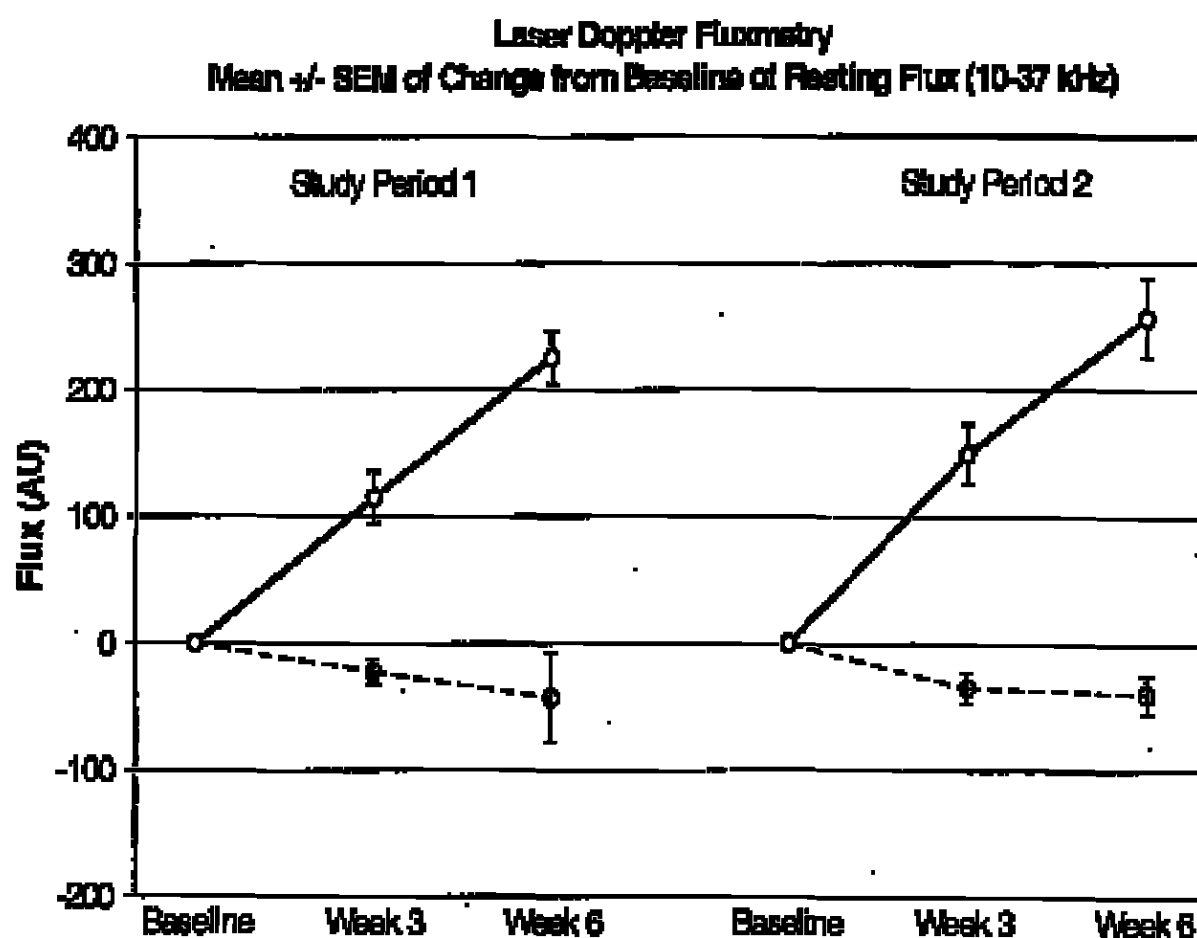
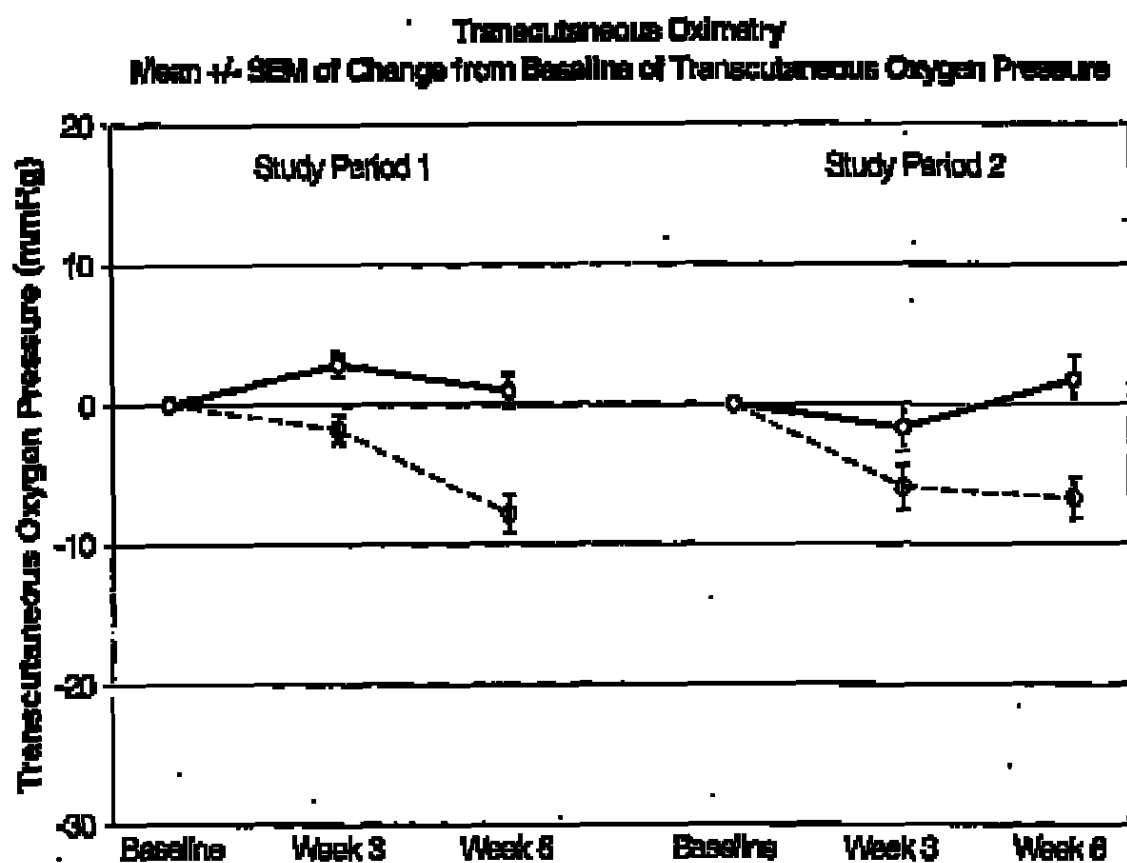


Fig. 2

5 **Fig. 3**

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| | | |
|---|---|--|
| Applicant's or agent's file reference
1-1445-PCT | FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. | |
| International application No.
PCT/EP 03/14148 | International filing date (day/month/year)
12/12/2003 | (Earliest) Priority Date (day/month/year)
31/12/2002 |
| Applicant
BOEHRINGER INGELHEIM INTERNATIONAL GMBH | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.
☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☐ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

4. With regard to the title,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

FILM COATED TABLET COMPRISING AN EXTRACT OF RED VINE LEAVES

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

✓

PCT/EP 03/14148

IPC 7 A61K9/28 A61K35/78

B. FIDELITY AND INTEGRITY

IPC 7 A61K

Electronic data have been collected during the International search phase of this study and, where practical, search terms which

EPO-Internal, WPI Data, PAJ, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Character of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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Further documents are listed in the continuation of box C.

Patients family members are tested in excess.

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Rate of the natural mortality of the larval stages

24 March 2004

Date of completion of the international search report

06/04/2004

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Fax (+31-70) 340-3710

Abstract

Loher, F.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/14148

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| BOEHRINGER INGELHEIM GMBH
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ALLEMAGNE | | 20. Feb. 2004 | | (PCT Rule 20.5(a)) | |
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| | | | Date of mailing (day/month/year) 12/02/2003 | | |
| Applicant's or agent's file reference 1-1445-PCT | | | IMPORTANT NOTIFICATION | | |
| International application No. PCT/RP03/14148 | | International filing date (day/month/year) 12/12/2003 | | Priority date (day/month/year) 31/12/2002 | |
| Applicant
BOEHRINGER INGELHEIM INTERNATIONAL GMBH | | | | | |
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PCT REQUEST

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1-1445-PCT

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| 0 | For receiving Office use only | |
| 0-1 | International Application No. | PCT/EP 03 / 14148 |
| 0-2 | International Filing Date | 12.12.03 12 DEC 2003 |
| 0-3 | Name of receiving Office and "PCT International Application" | EUROPEAN PATENT OFFICE
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| 0-7 | Applicant's or agent's file reference | 1-1445-PCT |
| I | Title of invention | FILM COATED TABLET |
| II | Applicant | |
| II-1 | This person is: | applicant only |
| II-2 | Applicant for | all designated States except US |
| II-3 | Name | BOEHRINGER INGELHEIM INTERNATIONAL GMBH |
| II-4 | Address: | Binger Strasse 173
D-55216 INGELHEIM AM RHEIN
Germany |
| II-5 | State of nationality | DE |
| II-6 | State of residence | DE |
| II-7 | Telephone No. | 06132/77-8884 |
| II-8 | Facsimile No. | 06132/77-4377 |
| III-1 | Applicant and/or inventor | |
| III-1-1 | This person is: | applicant and inventor |
| III-1-2 | Applicant for | US only |
| III-1-3 | Name (LAST, First) | BEPERKSTEN, Anke |
| III-1-4 | Address: | Rosmarthastrasse 84
D-55126 MAINZ
Germany |
| III-1-5 | State of nationality | DE |
| III-1-6 | State of residence | DE |

PCT REQUEST

1-1443-PCT

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| | | |
|----------------|--|--|
| II-2 | Applicant and/or inventor | |
| II-2-1 | This person is: | applicant and inventor |
| II-2-2 | Applicant for | US only |
| II-2-4 | Name (LAST, First) | SCHAEFER, Eckhard |
| II-2-5 | Address: | Richard-Wimmer-Strasse 23
D-63150 HEUSENSTADT
Germany |
| II-2-6 | State of nationality | DE |
| II-2-7 | State of residence | DE |
| III-3 | Applicant and/or inventor | |
| III-3-1 | This person is: | applicant and inventor |
| III-3-2 | Applicant for | US only |
| III-3-4 | Name (LAST, First) | SACHER, Fritz |
| III-3-5 | Address: | Kaiser-Karl-Strasse 27
D-68435 GUT-ALGENHEIM
Germany |
| III-3-6 | State of nationality | DE |
| III-3-7 | State of residence | DE |
| IV-1 | Agent or common representative; or address for correspondence
The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities on: | common representative |
| IV-1-1 | Name | BOEHRINGER INGELHEIM INTERNATIONAL GMBH |
| IV-1-2 | Address: | Binger Strasse 173
D-55216 INGELHEIM AM RHEIN
Germany |
| IV-1-3 | Telephone No. | 06132/77-8084 |
| IV-1-4 | Facsimile No. | 06132/77-4377 |

PCT REQUEST

1-1445-PCT

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| | | |
|---------------|---|--|
| V | Designation of States | |
| V-1 | Regional Patent
(other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned) | AP: BW GN GH KE LS MW MZ SD SL SZ TZ UG
ZN ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT
EA: AM AZ BY KG KE MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT
OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT |
| V-2 | National Patent
(other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned) | AE AG AL AM AT AU AZ BA BB BG BR BW BY
BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ
EC EE EG ES FI GB GD GE GH GM HR HU ID
IL IN IS JP KE KG KP KR KZ LC LK LR LS
LT LU LV MA MD MG MK MN MW MX MZ NI NO
NZ OM PG PH PL PT RO RU SC SD SE SG SK
SL SY TJ TM TN TR TT TZ UA UG US UZ VC
VN YU ZA ZN ZW |
| V-3 | Prosecution Designation Statement
In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 18 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. | |
| V-6 | Exclusion(s) from prosecution designations | NONE |
| VI-1 | Priority claim of earlier regional application | |
| VI-1-1 | Filing date | 31 December 2002 (31.12.2002) |
| VI-1-2 | Number | 02029108.4 |
| VI-1-3 | Regional Office | EP |

PCT REQUEST

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1-1445-PCT

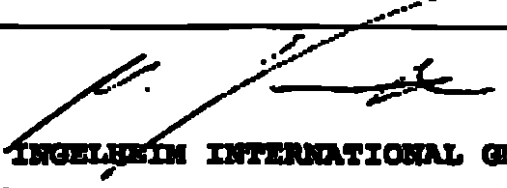
| | | | |
|--------|--|---|-----------------------------|
| VI-2 | Priority claim of earlier regional publication | | |
| VI-2-1 | Filing date | 05 September 2003 (05.09.2003) | |
| VI-2-2 | Number | 03019635.4 | |
| VI-2-3 | Regional Office | EP | |
| VII-1 | International Searching Authority Chosen | European Patent Office (EPO) (ISA/EP) | |
| VIII | Declarations | Number of declarations | |
| VIII-1 | Declaration as to the identity of the inventor | - | |
| VIII-2 | Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent | - | |
| VIII-3 | Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application | - | |
| VIII-4 | Declaration of inventorship (only for the purpose of the designation of the United States of America) | - | |
| VIII-5 | Declaration as to non-prejudicial disclosures or exceptions to lack of novelty | - | |
| IX | Check list | number of sheets | electronic file(s) attached |
| IX-1 | Request (including declaration sheet) | 5 | - |
| IX-2 | Description | 21 | - |
| IX-3 | Claims | 4 | - |
| IX-4 | Abstract | 1 | ABSTRACT.TXT |
| IX-5 | Drawings | 3 | - |
| IX-7 | TOTAL | 34 | |
| | Accompanying items | paper document(s) attached | electronic file(s) attached |
| IX-8 | Fee calculation sheet | ✓ | - |
| IX-9 | Original separate power of attorney | ✓ | - |
| IX-13 | Priority document(s) | Item(s) VI-1, VI-2 | - |
| IX-17 | PCT-EASY diskette | - | Diskette |
| IX-19 | Figure of the drawing which should accompany the abstract | | |
| IX-20 | Language of filing of the international application | English | |
| X-1 | Signature of applicant, agent or common representative | | |
| X-1-1 | Name | BOEHRINGER INGELHEIM INTERNATIONAL GMBH | |
| X-1-2 | Name of signatory | Dr. Klla | |
| X-1-3 | Capacity | ppa. | |

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1-1445-PCT

PCT REQUEST

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| | | |
|-------|--|--|
| X-2 | Signature of applicant, agent or common representative |  |
| X-2-1 | Name | BOEHRINGER INGELHEIM INTERNATIONAL GMBH |
| X-2-2 | Name of signatory | Dr. Kompter |
| X-2-3 | Capacity | i.V. |

FOR RECEIVING OFFICE USE ONLY

| | | |
|--------|---|------------------------|
| 10-1 | Date of actual receipt of the purported international application | 12.12.03 (12 DEC 2003) |
| 10-2 | Drawings: | |
| 10-2-1 | Received | |
| 10-2-2 | Not received | |
| 10-3 | Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application | |
| 10-4 | Date of timely receipt of the required corrections under PCT Article 11(2) | |
| 10-5 | International Searching Authority | ISA/EP |
| 10-6 | Transmittal of search copy delayed until search fee is paid | |

FOR INTERNATIONAL BUREAU USE ONLY

| | | |
|------|--|--|
| 11-1 | Date of receipt of the record copy by the International Bureau | |
|------|--|--|

PATENT COOPERATION TREATY

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PCT

From the INTERNATIONAL BUREAU

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

BOEHRINGER INGELHEIM INTERNATIONAL
GMBH
Binger Strasse 173
55218 INGELHEIM AM RHEIN
Germany

Date of mailing (day/month/year)

05 March 2004 (05.03.2004)

Applicant's or agent's file reference

1-1445-PCT

IMPORTANT NOTIFICATION

International application No.

PCT/EP2003/014148

International filing date (day/month/year)

12 December 2003 (12.12.2003)

International publication date (day/month/year)

Not yet published

Priority date (day/month/year)

31 December 2002 (31.12.2002)

Applicant

BOEHRINGER INGELHEIM INTERNATIONAL GMBH et al

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. (If applicable) The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
3. (If applicable) An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

| Priority date | Priority application No. | Country or regional Office
or PCT receiving Office | Date of receipt
of priority document |
|---------------------------|--------------------------|---|---|
| 31 Dec 2002 (31.12.2002) | 02029108.4 | EP | 20 Febr 2004 (20.02.2004) |
| 05 Sept 2003 (05.09.2003) | 03019636.4 | EP | 20 Febr 2004 (20.02.2004) |

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 338.88.76

Authorized officer

Aurora CENDANA (Fax : 338 89 75)

Telephone No. (41-22) 338 8905

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION TO THE DESIGNATED OFFICES

To:

BOEHRINGER INGELHEIM INTERNATIONAL GMBH
Binger Strasse 173
55216 INGELHEIM AM RHEIN
ALLEMAGNE

(PCT Rule 47.1(c), first sentence)

19. Juli 2004

| | | | |
|---|----|---------|----------|
| Date of mailing (day/month/year)
15 July 2004 (15.07.2004) | SB | gegeben | erledigt |
|---|----|---------|----------|

Applicant's or agent's file reference:
1-1445-PCT

IMPORTANT NOTICE

International application No.
PCT/EP2003/014148International filing date (day/month/year)
12 December 2003 (12.12.2003)Priority date (day/month/year)
31 December 2002 (31.12.2002)

Applicant

BOEHRINGER INGELHEIM INTERNATIONAL GMBH et al

ERFASST_{IV}

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 30, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:

AU, AZ, BY, CH, CN, CO, DZ, EP, HU, JP, KG, KP, KR, MD, MK, MZ, RU, TM, US

In accordance with Rule 47.1(c), third sentence, these Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and a copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE, AG, AL, AM, AP, AT, BA, BB, BG, BR, BW, BZ, CA, CR, CU, CZ, DE, DK, DM, EA, EC, EE, EG, ES, FI, GD, GE, GH, GM, HR, ID, IL, IN, IS, KE, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MG, MN, MW, MX, NI, NO, NZ, OA, OM, PG, PH, PL, PT, RO, SC, SD, SE, SG, SK, SL, SY, TJ, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 15 July 2004 (15.07.2004) under No. WO 2004/058227

4. **TIME LIMITS** for filing a demand for international preliminary examination and for entry into the national phase

The applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 30 MONTHS from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of 19 months from the priority date, but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see *PCT Gazette* No. 44/2001 of 1 November 2001, pages 19936, 19932 and 19934, as well as the *PCT Newsletter*, October and November 2001 and February 2002 issues.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (30, 21, 30 or 31 months, or other time limits), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

For filing a demand for international preliminary examination, see the *PCT Applicant's Guide*, Volume I/A, Chapter IX. Only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

It is the applicant's sole responsibility to monitor all these time limits.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Agnes Wittmann-Regis

Facsimile No. +41 22 740 14 35

Facsimile No. +41 22 338 89 70

Form PCT/IR/308 (April 2002)

28 Juli 2004

PATENT COOPERATION TREATY

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| | | |
|----|---------|----------|
| SB | 8535/04 | erladie. |
| 16 | | PCT |

From the INTERNATIONAL BUREAU

To:

BOEHRINGER INGELHEIM INTERNATIONAL
GMBH
Binger Strasse 173
55218 INGELHEIM AM RHEIN
Germany

**INFORMATION CONCERNING ELECTED
OFFICES NOTIFIED OF THEIR ELECTION**

(PCT Rule 61.3)

| | | |
|---|---|---|
| Date of mailing (day/month/year)
12 July 2004 (12.07.2004) | | IMPORTANT INFORMATION |
| Applicant's or agent's file reference
1-1445-PCT | | |
| International application No.
PCT/EP2003/014148 | International filing date (day/month/year)
12 December 2002 (12.12.2002) | Priority date (day/month/year)
31 December 2002 (31.12.2002) |
| Applicant
BOEHRINGER INGELHEIM INTERNATIONAL GMBH et al | | |

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

EP : AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE,
SI, SK, TR
National : BG, CA, CN, CZ, DE, JP, KP, KR, MN, NO, PL, RO, RU, SK, US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

AP : BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW
EA : AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
OA : BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
National : AE, AG, AL, AM, AT, AU, AZ, BA, BB, BR, BW, BY, BZ, CH, CO, CR, CU, DK, DM, DZ, EG,
EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KZ, LC, LK, LR, LS, LT, LU,
LV, MA, MD, MG, MK, MW, MX, MZ, NI, NZ, OM, PG, PH, PT, SC, SD, SE, SG, SL, SY, TJ, TM, TN, TR,
TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

3. The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and (furnishing, if required, a translation of the international application (Article 3911(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

Some offices have fixed time limits, expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

The entry into the European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent.

| | |
|---|--|
| The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland | Authorized officer:

Maria KIRCHNER (Fax 338 8970) |
| Facsimile No. (41-22) 338.60.70 | Telephone No. (41-22) 338.4466 |

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ EP

PCT

DEMAND

under Article 31 of the Patent Cooperation Treaty:

The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty.

| | |
|--|--|
| For International Preliminary Examining Authority use only | |
| Identification of IP EA | Date of receipt of DEMAND |
| Box No. 1 IDENTIFICATION OF THE INTERNATIONAL APPLICATION | |
| Applicant's or agent's file reference
Case 1/1445-PCT | |
| International application No.
PCT/EP03/14148 | International filing date (day/month/year)
12/12/2003 |
| (Earliest) Priority date (day/month/year)
31/12/2002 | |
| Title of invention:
FILM COATED TABLET | |
| ERFASST | |
| Box No. II APPLICANT(S) | |
| Name and address: (Family name followed by given names; for a legal entity, full official designation. The address must include postal code and name of country.)
Boehringer Ingelheim International GmbH
Binger Strasse 173
55216 Ingelheim am Rhein
DE | |
| Telephone No.
06132-77-8884 | |
| Facsimile No.
06132-77-4377 | |
| Telex/Teletype No. | |
| Applicant's registration No. with the Office | |
| State (that is, country) of nationality:
DE | State (that is, country) of residence:
DE |
| Name and address: (Family name followed by given names; for a legal entity, full official designation. The address must include postal code and name of country.)
Anke ESPERESTER
Rosmerthastrasse 84
55126 Mainz
DE | |
| State (that is, country) of nationality:
DE | State (that is, country) of residence:
DE |
| Name and address: (Family name followed by given names; for a legal entity, full official designation. The address must include postal code and name of country.)
Eckhard SCHAEFER
Richard-Wimmer-Strasse 23
63150 Heusenstamm
DE | |
| State (that is, country) of nationality:
DE | State (that is, country) of residence:
DE |
| ☒ Further applications are indicated on a continuation sheet. | |

Sheet No. 2

International Application No.
PCT/EP03/14148

Continuation of Box No. 8 APPLICANT(S)

If more of the following sub-forms is used, this sheet should not be included in the demand

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address may include postal code and name of country)*

Fritz SACHER
Kaiser-Karl-Strasse 27
55435 Gau-Algesheim
DE

State (this is, country) of nationality:
DE

State (this is, country) of residence:
DE

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address may include postal code and name of country)*

State (this is, country) of nationality:

State (this is, country) of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address may include postal code and name of country)*

State (this is, country) of nationality:

State (this is, country) of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address may include postal code and name of country)*

State (this is, country) of nationality:

State (this is, country) of residence:

☐ Further applicants are indicated on another continuation sheet.

Sheet No. 3

International application No.
PCT/EP03/14148

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☐ agent ☒ common representative
and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.
☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.
☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: (Please give fully by given name; for a legal entity, full official designation.
The address must include postal code and name of country.)

Boehringer Ingelheim International GmbH
Binger Strasse 173
55216 Ingelheim am Rhein
DE

Telephone No.

06132-77-8884

Facsimile No.

06132-77-4377

Teleprinter No.

Agent's registration No. with the Office

☐ Address for correspondence: Mark this check-box where no agent or common representative has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statements concerning amendments:

1. The applicant wishes the international preliminary examination to start on the basis of:

☐ the international application as originally filed

the description ☐ as originally filed
☐ as amended under Article 34

the claims ☐ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34

the drawings ☐ as originally filed
☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of the applicable time limit under Rule 59.1(d).

4. ☐ The applicant expressly wishes the international preliminary examination to start earlier than at the expiration of the applicable time limit under Rule 54.5a.1(a).

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination English

☒ which is the language in which the international application was filed.

☐ which is the language of a translation furnished for the purposes of international search.

☐ which is the language of publication of the international application.

☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The filing of this demand constitutes the election of all Contracting States which are designated and are bound by Chapter II of the PCT.

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | |
|---|---|--------|
| 1. translation of international application | : | sheets |
| 2. amendments under Article 34 | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of specification under Article 19 | : | sheets |
| 5. letter | : | sheet |
| 6. other (specify) | : | sheet |

For International Preliminary Examining Authority use only
received not received

- | | |
|--------------------------|--------------------------|
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |

The demand is also accompanied by the item(s) marked below:

- | | |
|---|--|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listing in computer readable form |
| 3. ☐ original general power of attorney | 7. ☐ tables in computer readable form related to a sequence listing |
| 4. ☐ copy of general power of attorney; reference number, if any | 8. ☐ other (specify): |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

Boehringer Ingelheim International GmbH

ppa.


Dr. Klein


Dr. Weymann

For International Preliminary Examining Authority use only

1. Date of receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.4(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.
☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the time limit of 19 months from the priority date as extended by virtue of Rule 50.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 52.

6. ☐ The date of receipt of the demand is AFTER the expiration of the time limit under Rule 54bis.1(a) and item 7 or 8, below, does not apply.
7. ☐ The date of receipt of the demand is WITHIN the time limit under Rule 54bis.1(a) as extended by virtue of Rule 50.5.
8. ☐ Although the date of receipt of the demand is after the expiration of the time limit under Rule 54bis.1(a), the delay in arrival is EXCUSED pursuant to Rule 52.

For International Bureau use only

Demand received from IPEA on:

PCT

FEE CALCULATION SHEET

Annex to the Demand

| | |
|---|---|
| International application No. PCT/EP03/14148 | For International Preliminary Examining Authority use only |
| Applicant's or agent's file reference Case 1/1445-PCT | Date stamp of the IPEA |
| Applicant
Boehringer Ingelheim International GmbH | |
| CALCULATION OF PRESCRIBED FEES | |
| 1. Preliminary examination fee | 1.530 € P |
| 2. Handling fee (Applicants from certain States are entitled to a reduction of 25% of the handling fee. Where the applicant is for all applicants are) to entitled, the amount to be entered at H is 25% of the handling fee.) | 129 € H |
| 3. Total of prescribed fees
Add the amounts entered at P and H
and enter total in the TOTAL box | <div style="border: 1px solid black; padding: 5px; width: fit-content; margin: 0 auto;"> 1.659 € </div> <div style="border: 1px solid black; padding: 5px; width: fit-content; margin: 0 auto;"> TOTAL </div> |
| MODE OF PAYMENT | |
| ☒ authorization to charge deposit account with the IPEA (see below) | ☐ cash |
| ☐ cheque | ☐ revenue stamps |
| ☐ postal money order | ☐ coupons |
| ☐ bank draft | ☐ other (specify): |
| AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT
<i>(This mode of payment may not be available in all IPEAs)</i> | |
| ☒ Authorization to charge the total fees indicated above. | IPEA EP |
| ☒ (This check-box may be marked only if the conditions for deposit accounts of the IPEA to permit Authorization to charge any deficiency or credit any overpayment in the total fees indicated above. | Deposit Account No.: 2800.0140 |
| | Date: June 7, 2004 |
| | Name: Boehringer Ingelheim GmbH |
| | Signature: |
| | Dr. Marc |



Boehringer
Ingelheim

66

Boehringer Ingelheim International GmbH - 55216 Ingelheim am Rhein

Europäisches Patentamt
Erhardstrasse 27

80331 München

Boehringer Ingelheim
International GmbH

07 June 2004

International patent application No. PCT/EP 03/14148
Our Ref.: Case 1/1445-PCT

Demand under Art.31 PCT

Applicant hereby submits the Demand under Art.31 PCT,

Furthermore, the applicant requests that the EPO as the competent International Preliminary Examination Authority refrains from the "procedure without detailed substantive examination" but directly conducts the "detailed substantive examination" of the subject application.

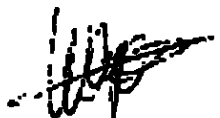
Our reference
Ko/ml - P01-1444

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ppa. I.V.


Dr. Klits


Dr. Weymann

Encl.:
Demand under Art.31 PCT

Board of Managing Directors
Dr. Alessandro Bianchi
(Chairman)
Dr. Dr. Andreas Bamer
(Vice Chairman)
Dr. Hans-Jürgen Leuchs
Prof. Dr. Marbod Muff

Seat Ingelheim am Rhein
Commercial Register
Bingen HR II 1063

Deutsche Bank AG
BLZ 550 700 40
Account No. 0122 580
Swifts DEUTDE33

PATENT CO PERATION TREATY

67.

Eingang CD Patents

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

06. Juli 2004

PCT

To:

BOEHRINGER INGELHEIM INTERNATIONAL
GMBH
Binger Strasse 173
D-55216 Ingelheim am Rhein
ALLEMAGNE

SB gesehen erledigt

16

NOTIFICATION OF RECEIPT
OF DEMAND BY COMPETENT INTERNATIONAL
PRELIMINARY EXAMINING AUTHORITY

(PCT Rules 59.3(c) and 61.1(b), first sentence
and Administrative Instructions, Section 601(a))

Date of mailing
(day/month/year)

05-07-2004

Applicant's or agent's file reference
Case 1/1445-PCT

IMPORTANT NOTIFICATION

International application No.

PCT/EP03/14148

International filing date (day/month/year)

12/12/2003

Priority date (day/month/year)

31/12/2002

Applicant

BOEHRINGER INGELHEIM INTERNATIONAL GMBH et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

09/06/2004

2. This date of receipt is:

- ☒ the actual date of receipt of the demand by this Authority (Rule 61.1(b)).
☐ the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(a)).
☐ the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. ☐ **ATTENTION:** This date of receipt is after the expiration of 19 months from the priority date. Consequently, in respect of some Offices, the demand does not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)) and the acts for entry into the national phase must therefore be performed within 13 months from the priority date (or later in some Offices). However, in respect of some other Offices, the time limit of 30 months (or later) may nevertheless apply. See the Annex to Form PCT/IPEA/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

- ☐ (If applicable) This notification confirms the information given by telephone, facsimile transmission or in person on:

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/



European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0, Tx: 523656 apma d
Fax: (+49-89) 2399-4445

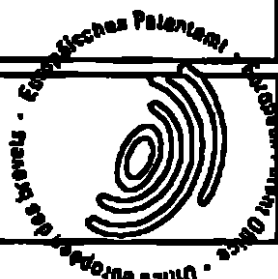
Authorized officer

LODOLO F

Tel. (+49-89) 2399-2039

Form PCT/IPEA/402 (April 2002; reprint January 2004)

(30/06/2004)



From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

| | | | | | | | | | | |
|---|--|---|--|------------|---------|----------|----|---|--|--|
| To: | | Eingang CD Patents | | PCT | | | | | | |
| BOEHRINGER INGELHEIM
INTERNATIONAL GMBH
Binger Strasse 173
D-55216 Ingelheim am Rhein
ALLEMAGNE | | 02. März 2005 | | | | | | | | |
| | | NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1) | | | | | | | | |
| | | <table border="1"> <tr> <td>SB</td> <td>gesehen</td> <td>erledigt</td> </tr> <tr> <td>40</td> <td>✓</td> <td></td> </tr> </table> | | SB | gesehen | erledigt | 40 | ✓ | | |
| SB | gesehen | erledigt | | | | | | | | |
| 40 | ✓ | | | | | | | | | |
| | | Date of mailing
(day/month/year) | | 01.03.2005 | | | | | | |
| Applicant's or agent's file reference
Case 1/445-PCT | | IMPORTANT NOTIFICATION | | | | | | | | |
| International application No.
PCT/EP 03/14148 | International filing date (day/month/year)
12.12.2003 | Priority date (day/month/year)
31.12.2002 | | | | | | | | |
| Applicant
BOEHRINGER INGELHEIM INTERNATIONAL GMBH et al. | | | | | | | | | | |

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed invention is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

| | | |
|--|--|---|
| Name and mailing address of the international
preliminary examining authority:

 European Patent Office
D-80296 Munich
Tel. +49 89 2399-0 Tlx 523656 eppo d
Fax: +49 89 2399-4465 | Authorized Officer

Senkel, H

Tel. +49 89 2399-8071 |  |
|--|--|---|

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

| | | | | |
|---|--|---|--|---|
| Applicant's or agent's file reference
Case 1/1445-PCT | | FOR FURTHER ACTION | | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/10) |
| International application No.
PCT/EP 03/14148 | | International filing date (day/month/year)
12.12.2003 | | Priority date (day/month/year)
31.12.2002 |
| International Patent Classification (IPC) or both national classification and IPC
A61K928 | | | | |
| Applicant
BOEHRINGER INGELHEIM INTERNATIONAL GMBH et al. | | | | |
| <p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p>☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p> | | | | |
| <p>3. This report contains indications relating to the following items:</p> <p>I ☒ Basis of the opinion</p> <p>II ☐ Priority</p> <p>III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p>IV ☐ Lack of unity of invention</p> <p>V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p>VI ☐ Certain documents cited</p> <p>VII ☐ Certain defects in the international application</p> <p>VIII ☐ Certain observations on the international application</p> | | | | |
| Date of submission of the demand

09.06.2004 | | Date of completion of this report

01.03.2005 | | |
| Name and mailing address of the international preliminary examining authority:
 European Patent Office
D-60298 Munich
Tel. +49 89 2369 - 0 Tlx 323666 epmu d
Fax: +49 89 2369 - 4465 | | Authorized Officer

Loher, F
Telephone No. +49 89 2369-7639
 | | |

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/14148

I. Basis of the report

1. With regard to the elements of the International application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-22 as originally filed

Claims, Numbers

1-10 as originally filed

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the International application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the International application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 03/14148**

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

1. Statement

| | | |
|--------------------------------------|--------------------|-------------------|
| Novelty (N) | Yes: Claims | 1-13,15,16 |
| | No: Claims | 14 |
| Inventive step (IS) | Yes: Claims | |
| | No: Claims | 1-16 |
| Industrial applicability (IA) | Yes: Claims | 1-16 |
| | No: Claims | |

2. Citations and explanations

see separate sheet

The following documents (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

- D1: US-B1-6 485 727 (FREY HANS W ET AL) 26 November 2002 (2002-11-26)
D2: WO 01 28363 A (FREY HANS W ;ESPERESTER ANKE (DE); VIX JEAN MICHEL (DE); BOEHRINGE) 26 April 2001 (2001-04-26) cited in the application
D3: US-B1-6 297 218 (MORAZZONI PAOLO ET AL) 2 October 2001 (2001-10-02)
D4: US-A-4 897 270 (DEUTSCH DAVID S ET AL) 30 January 1990 (1990-01-30)
D5: WO 02 072118 A (MOURA ROBERTO SOARES ;UNIV DO ESTADO DO RIO DE JANEI (BR)) 19 September 2002 (2002-08-19)

If not mentioned otherwise, the relevant passages are those mentioned in the European Search Report.

Art 33(2) The present application does not meet the requirements of Article 33(2) PCT, since the subject-matter of claim 14 is not new.

D1 and D2 describe an aqueous extract of red vine leaves obtainable by a method comprising the steps (a)-(e) as defined by present claim 14. Optionally silicon dioxide is added to the extract to facilitate the further processing of the extract (see e.g. D1, column 3, 4th paragraph). As present claim 14 defines step (f) as "... addition of up to 10% of a flow regulator..." (i. e. 0-10%) this feature is also considered to be optional. Therefore, the subject-matter of claim 14 is not new in the light of D1 or D2.

Art 33(3) The present application does not meet the requirements of Article 33(3) PCT, because the subject-matter of claims 1-16 does not involve an inventive step in the sense of Article 33(3) PCT.

D1, which is considered to represent the most relevant state of the art, discloses the manufacture of an aqueous extract of red vine leaves which is used in the present application. D1 furthermore suggests to prepare solid administration

forms such as coated tablets and mentions excipients used in the present application including silicon dioxide. The content of extract in those solid administration forms is within the same range as disclosed in the present application. The use of the extract is exactly the same as disclosed in the present application.

The problem to be solved by the present invention may therefore be regarded as how to provide a stable and swallowable coated tablet containing at least 50% of the active ingredient.

The present application suggests to solve the problem posed by providing a film coated tablet containing at least 50% (w/w) of a dried aqueous extract of vitis vinifera, up to 50% (w/w) excipients and a tablet film.

Yet, D4 teaches the manufacture of film coated tablets having a core which comprises about 80% active agent (in a similar absolute amount) and ingredients in similar amounts as used in the present application. The coating is made by using hypromellose as film former, propylene glycol as plastiziser and opaspray as coating and colouring agent.

D5 discloses the use of aerosil in order to facilitate the processing of and in order to stabilize an extract of vitis vinifera.

Taking into account the teaching of the cited prior art the following reasoning applies:

There seems to be no basis for inventive step within the present application as filed since no evidence can be found that the features which are novel over the prior art result in a solution of the posed problem which could not have been foreseen by the skilled person.

It is therefore noted, that the solution proposed in claims 1-16 of the present application is not considered to be inventive in the sense of Article 33(3) PCT.

Art 33(4) The subject-matter of claims 1-16 is considered to be industrially applicable in the sense of Art 33(4) PCT.

Comprimido recubierto con una película

ANTECEDENTES DE LA INVENCION

1. CAMPO TÉCNICO

5 La invención se refiere a un comprimido recubierto con una película que comprende un extracto seco de hojas de parra roja, un excipiente y una película del comprimido y su uso para la mejora de la circulación sanguínea y/o el suministro de oxígeno a las extremidades inferiores.

2. INFORMACIÓN ANTERIOR

10 La insuficiencia venosa crónica (CVI) es una enfermedad progresiva y puede llevar en muchos pacientes (especialmente si no están tratados) a edema, plebectasia coronaria (Widmer etapa I), hiperpigmentación, induración, lipodermatosclerosis, atrofia blanca (Widmer etapa II), o úlceras varicosas en las piernas (Widmer etapa III). La hemodinámica alterada crónicamente en las venas profundas o superficiales debido a segmentos venosos obstruidos o a la incompetencia valvular lleva usualmente a
15 enfermedades de la piel en el área interior del tobillo o en las extremidades inferiores. Se ha considerado que las alteraciones en la microcirculación de la piel son aportaciones principales para los cambios de la piel asociados con la hipervolemia venosa crónica y la hipertensión venosa. (por ejemplo, Fagrell B. *Vital microscopy and the pathophysiology of deep venous insufficiency. Int Angiol* 1995;14:18-22; Jünger M, Klyscz T, Hahn M, Rassner G. *Disturbed blood flow regulation in venous leg ulcers. Int J. Microcirc* 1996;16:259-265).

20 Obviamente, la microangiopatía cutánea de relevancia clínica tal como los capilares dilatados, tortuosos alrededor del microedema contribuye a las alteraciones de la piel en las extremidades inferiores y determina el curso de CVI (Fagrell B, Loc. Cit. and Jünger M et al., loc. Cit.).

25 La aplicación de la técnica láser Doppler en las alteraciones venosas está bien ilustrada (por ejemplo, Tulevski II, Ubbink DT, Jacobs MJHM. *Red and green laser Doppler compared with capillary microscopy to assess skin microcirculation in the feet of healthy subjects. Microvasc Res* 1999;58(2):83-88 and Bollinger A, Jäger K, Jünger K, Selfert H. *The vascular laboratory: advances in non-invasive techniques. World J Surg* 1988;12:724-731).

30 Se han desarrollado diferentes técnicas para investigar la microcirculación en ambas capas de la piel diferentes funcionalmente: la más profunda, la capa principalmente termoreguladora y la capa superficial, nutritiva. Las alteraciones microcirculatorias en la capa nutritiva superficial son de suma relevancia para los cambios de la piel tróficos. (Jünger M et al., loc. Cit. And Gechwadtner ME, Ambrozy E,

Fasching S, Willfort A, Schneider B, Böhler K, et al. *Microcirculation in venous ulcers and surrounding skin: findings with capillary microscopy and laser Doppler imager. Eur J Clin Invest* 1999;29:706-716).

5 La patente británica GB 934.554 describe que la resistencia capilar en cobayas deficientes en vitamina A se puede mejorar por la administración intraperitoneal de un extracto alcohólico de hojas de parra.

10 La solicitud de patente internacional WO 01/28383 describe un método para la prevención o alivio de la incomodidad asociada con la insuficiencia venosa crónica de media a moderada de las extremidades inferiores con la ayuda de un extracto acuoso de hojas de parra roja. Adicionalmente se sugiere una pauta de dosificación diaria de 80 a 1000 mg divididos en 1 hasta 3 cápsulas.

15 El problema subyacente en la presente invención fue proporcionar una forma farmacéutica que permita administrar tales altas cantidades de extracto acuoso de hojas de parra roja con la pauta sugerida. En vista del acuerdo del paciente existe el requerimiento de que tales formas farmacéuticas no deban ser muy altas, para facilitar su ingestión. Por otro lado la forma farmacéutica debe tener una alta estabilidad para asegurar largos tiempos de almacenaje. Además, la alta biodisponibilidad es un prerrequisito para el éxito terapéutico o preventivo de tal forma farmacéutica.

BREVE SUMARIO DE LA INVENCION

20 Se ha encontrado sorprendentemente que un comprimido recubierto con una película comprende:

(a) al menos 50 % en peso de extracto seco de hojas de parra roja, que es obtenible por extracción de hojas de parra roja con agua y secado;

25 (b) hasta 50 % en peso de un excipiente que consta esencialmente de
- al menos un aglutinante,
- al menos un desintegrante,
- al menos un agente de carga, y
- al menos un lubricante; y

30 (c) una película del comprimido que consta esencialmente de un formador de película, un plastificante, un agente de revestimiento y opcionalmente un agente colorante;

satisface estos requerimientos y se puede usar para mejorar significativamente la microcirculación y el suministro de oxígeno en el área perimaleolar predominantemente afectada con CVI de la pierna en los pacientes.

35 Por consiguiente la invención se refiere a un comprimido recubierto con una película que comprende los siguientes constituyentes:

(a) al menos 50 % en peso de extracto seco de hojas de parra roja, que es obtenible por extracción de hojas de parra roja con agua y secado;

(b) hasta 50 % en peso de un excipiente que consta esencialmente de

- al menos un aglutinante,
- al menos un desintegrante,
- al menos un agente de carga, y
- al menos un lubricante; y

(c) una película del comprimido que consta esencialmente de un formador de película, un plastificante, un agente de revestimiento y opcionalmente un agente colorante;

Otro aspecto de la presente invención es un procedimiento para preparar tal comprimido recubierto con una película que comprende las etapas de:

(A) mezclar el extracto acuoso seco de hojas de parra roja (a) con los excipientes (b), opcionalmente en presencia de un diluyente volátil;

(B) opcionalmente cribar la mezcla obtenida;

(C) comprimir la mezcla con una prensa para comprimidos adecuada; y

(D) revestir el comprimido resultante con una película para comprimidos (c).

Además, la invención se refiere al uso de tal comprimido revestido con una película para preparar una composición farmacéutica o dietética para el tratamiento o prevención de la incomodidad, trastorno y/o enfermedad asociada con la hipervolemia venosa crónica y la hipertensión venosa.

Además, la invención se refiere a un extracto acuoso de hojas de parra roja que es obtenible por un método que comprende las etapas de:

(a) recolectar las hojas de parra roja en un momento en el que el contenido de flavonoides haya alcanzado un óptimo;

(b) secar y prensar las hojas;

(c) cortar las hojas en trozos;

(d) extraer las hojas con agua a elevadas temperaturas durante 6 a 10 horas;

(e) concentrar y secar el extracto obtenido, y

(f) añadir hasta 10 % en peso de sílice en relación con la cantidad final total del extracto resultante.

BREVE DESCRIPCIÓN DE LOS DIBUJOS

La Figura 1 muestra el modelo esquemático del estudio clínico llevado a cabo para probar la eficacia del comprimido revestido con una película según la presente invención.

La Figura 2 muestra la influencia del extracto de hojas de parra que contiene el comprimido revestido con una película

—○— AS195 360 mg comparado con

—○— placebo

5 sobre la microcirculación medida con flujometría de láser Doppler (LDF 10-37 kHz).

La Figura 3 muestra la influencia del extracto de hoja de parra que contiene el comprimido revestido con una película

—○— AS195 360 mg comparado con

—○— placebo

10 sobre la presión parcial de oxígeno transcutáneo (tpO_2)

DESCRIPCIÓN DETALLADA DE LA INVENCION

15 El comprimido revestido en forma de película de la presente invención consta de ingredientes herbales derivados por extracción acuosa de hojas de parra roja (*folia vitis viniferae*; Extractum *Vitis viniferae* a folium spissum et siccum) y secado (a), excipientes (b) y la película del comprimido (c). Este extracto contiene flavon(ol)-glicosidos, -glucuronidos y flavonoides, con quercetina-3-O-β-D-glucuronida e isoquercitrina (quercetina-3-O-β-glucosido) como sus ingredientes activos principales.

20 Todavía no se ha elucidado totalmente el ámbito de sus acciones farmacológicas, pero los estudios *in vitro* indican que tienen propiedades antioxidantes y antiinflamatorias y que inhiben la agregación de las plaquetas y la hialuronidasa y el edema reducido, posiblemente reduciendo la permeabilidad capilar. Experimentos preclínicos *in vivo* demostraron efectos antiinflamatorios y espesantes del muro capilar.

25 El comprimido revestido con una película según la presente invención comprende de 50 a 70% de extracto de hoja de parra roja acuoso seco con un alto contenido de flavonoides de 2-15%.

30 Como norma la relación en peso entre el extracto seco y los excipientes usados para producir el núcleo de los comprimidos está entre 1 : 1 a 2 : 1, preferiblemente entre 1,1 : 1 y 1,8 : 1, en particular entre 1,25 : 1 y 1,75 : 1.

Un comprimido revestido con una película que comprende

(a) de 50 a 70 % en peso de dicho extracto seco de hojas de parra roja;

(b) de 25 a 49 % en peso de dicho excipiente, y

(c) de 1 a 5 % en peso de dicha película del comprimido,

35 basado en la masa total del comprimido revestido con una película.

Más preferido es un comprimido revestido con una película que comprende (a) de 51 a 59 %, en particular aproximadamente 55 % en peso de dicho extracto seco de hojas de perra roja;

(b) de 38 a 48 %, en particular aproximadamente 43 % en peso de dicho excipiente, y

5 (c) de 1 a 3 %, en particular aproximadamente 2,7 % en peso de dicha película del comprimido,

basado en la masa total del comprimido revestido con una película.

Otra realización preferida es un comprimido revestido con una película, en el que el excipiente (b) consta esencialmente de

- 10 - de 70 a 85 % en peso de al menos un aglutinante,
- de 0,5 a 12,5 % en peso de al menos un desintegrante,
- de 5 a 15 % en peso de al menos un agente de carga, y
- de 1 a 5 % en peso de al menos un lubricante,

basado en la masa total los excipientes reunidos.

15 El término "aglutinante" como se usa anterior y posteriormente significa un excipiente que es adecuado para aglutinar unos componentes con otros. Los aglutinantes preferidos según la invención se seleccionan entre:

20 Celulosa en polvo, celulosa microcristalina, sorbitol, almidón, polivinilpirrolidona (povidona), copolímeros de vinilpirrolidona con otros derivados vinílicos (copovidona), derivados de celulosa, particularmente metilhidroxipropilcelulosa, por ejemplo, Methocel A 15 LV, y mezclas de estos compuestos. Los aglutinantes preferidos son celulosa en polvo, particularmente celulosa microcristalina y/o copovidona. Si se usan los aglutinantes mencionados antes, la cantidad en peso, basado en la masa total del comprimido según la invención, está preferiblemente en el intervalo de 15-45 % en peso, más preferiblemente 25-40 % en peso, lo más preferiblemente aproximadamente 33 % en peso. Gracias al aglutinante de celulosa microcristalina particularmente preferido, los comprimidos que se obtienen tienen una alta estabilidad y son bien aceptados por los pacientes a los que se les administra el extracto de hojas de perra roja.

30 El comprimido según la invención contiene también desintegrantes además de los ingredientes mencionados antes. Dentro del alcance de la invención estos desintegrantes pueden ser conocidos también opcionalmente como agentes de rotura. Estos se seleccionan preferiblemente, según la invención, entre glicolato de almidón y sodio, polivinilpirrolidona reticulada (crospovidona), sal de croscarmelosa de sodio (sal de sodio de carboximetiléter-celulosa, reticulada), carboximetilcelulosa de sodio, almidón de maíz seco, sílica coloidal anhidra y sus mezclas. Dentro del alcance de la

presente invención se prefiere particularmente el uso de glicolato de almidón y sodio, crospovidona y, preferiblemente la sal de sodio de la crospovidona o croscarmelosa y la sílica coloidal anhidra. Lo más preferido es una mezcla de croscarmelosa de sodio, sílica coloidal anhidra y opcionalmente crospovidona. Si se usan los desintegrantes mencionados antes, la cantidad en peso, basado en la masa total del comprimido según la invención, está preferiblemente en el intervalo de aproximadamente 0,5-10 % en peso, más preferiblemente aproximadamente 1,5-7,5 % en peso. Gracias a la combinación particularmente preferida de desintegrantes, los comprimidos que se obtienen tienen una alta estabilidad y proporcionan alta biodisponibilidad al extracto acuoso de hojas de parra roja.

El comprimido según la invención también contiene un agente de carga. Como norma los agentes de carga son compuestos inertes tales como óxidos de metales inorgánicos o fosfato inorgánico o fosfato de hidrógeno. Preferiblemente el agente de carga es un fosfato de hidrógeno de calcio anhidro. Si se usan los agentes de carga mencionados antes, la cantidad en peso, basada en la masa total del comprimido según la invención, está preferiblemente en el intervalo de aproximadamente 1-10 % en peso, más preferiblemente aproximadamente 2-8 % en peso.

El comprimido según la invención contiene también agentes de flujo o reguladores de flujo y también lubricantes, como ingredientes adicionales. Estos incluyen, dentro del alcance de la presente invención, por ejemplo, dióxido de sílica, talco, ácido esteárico, estearilfumarato de sodio, estearato de magnesio, y tribehenato de glicerol. Según la invención se usa preferiblemente el estearato de magnesio. Si se usan los lubricantes preferidos mencionados antes, su cantidad en peso, basada en la masa total del comprimido según la invención, está preferiblemente en el intervalo de aproximadamente 0,1-10 % en peso, preferiblemente aproximadamente 0,5-5 % en peso, más preferiblemente entre 0,8 y 1,5 % en peso.

Se prefiere adicionalmente un comprimido revestido con una película, en el que la película del comprimido (c) consta esencialmente de:

- 50 a 85 % en peso de al menos un formador de película,
- 5 a 10 % en peso de al menos un plastificante,
- 10 a 20 % en peso de al menos un agente de revestimiento tal como talco, y
- 0 a 15 % en peso de al menos un colorante.

Basado en la masa total de la película del comprimido (c).

La película del comprimido según la invención puede contener también uno o más colorantes sintéticos o naturales, farmacéuticamente aceptables, preferiblemente

uno o más óxidos de metales inorgánicos tales como dióxido de titanio (E 171) y/o óxido férrico (E 172). Si se usan los colorantes preferidos mencionados antes su cantidad en peso basada en la masa total del comprimido según la invención es de 0,01 a 0,5 % en peso.

5 Es un objetivo adicional de la presente invención proporcionar un comprimido revestido con una película para prevenir y/o aliviar la incomodidad asociada con la insuficiencia venosa crónica de media a moderada de la extremidades inferiores que comprende ingredientes herbales, donde el comprimido se prepara con arreglo a un procedimiento controlado que preserve las cualidades curativas herbales de los
10 ingredientes.

 Es un objetivo adicional de la presente invención proporcionar una composición que sea efectiva en prevenir y/o aliviar la incomodidad asociada con la insuficiencia venosa crónica de media a moderada de las extremidades inferiores.

 Es un objetivo adicional añadido de la presente invención proporcionar un
15 comprimido revestido con una película que sea efectivo en prevenir y/o aliviar la incomodidad asociada con la insuficiencia venosa crónica de media a moderada de las extremidades que comprende ingredientes herbales y que tiene mínimos efectos secundarios o no los tiene y por tanto es segura para consumo interno y tiene una alta estabilidad y tiene una alta aceptación por parte de los pacientes.

20 El extracto acuoso preparado a partir de las hojas de parra roja se caracteriza por un alto contenido de 2 a 20 %, preferiblemente de 2 a 10 % de flavonoides biológicamente activos.

 El término "una persona que lo necesita" o "paciente" se refiere anterior y posteriormente a una persona femenina o masculina que padece de etapas tempranas
25 clínicamente no relevantes de insuficiencia venosa crónica (CVI) o que se ha demostrado en él la etapa I y II de CVI según Widmer. Por norma tales pacientes son gente mayor con una edad entre 30 y 80, preferiblemente entre 32 y 76 años, teniendo una edad media ($\pm$ desviación estándar) de 55,2 $\pm$ 7,7 años. Por norma CVI aparece más en pacientes femeninos que en pacientes masculinos

30 Para que esta invención sea completamente entendida, se exponen los siguientes ejemplos. Estos ejemplos tienen el propósito de ilustrar las realizaciones de esta invención, y no se deben tomar como limitantes del alcance de esta invención de ningún modo.

 Los ejemplos que siguen son ilustrativos, como puede reconocer un experto en
35 la técnica, y las condiciones particulares se pueden modificar como se necesita para las composiciones individuales. Los materiales usados en los ensayos posteriores

están o comercialmente disponibles o se pueden preparar fácilmente a partir de materiales comercialmente disponibles por los expertos en la técnica.

La base del comprimido es el extracto acuoso de hojas de parra roja (*foliae vitis viniferae* L.). El material de partida para la preparación del extracto son hojas de parra roja recogidas en un momento en el que el contenido de flavonoides ha alcanzado un óptimo. Este es el caso realmente durante el tiempo de cosecha de las uvas. Las hojas se secan y prensan cuidadosamente. Para la extracción las hojas se cortaron en piezas de 5 a 10 mm preferiblemente. Para lograr un alto contenido de flavonoides se realiza la extracción a elevada temperatura, preferiblemente a una temperatura en el intervalo de 50° a 80°C, durante un tiempo de al menos 6 hasta 10 horas. El método preferido es en el que se realiza un filtrado exhaustivo.

El así denominado extracto fluido obtenido en el curso de la extracción se concentra mediante el uso de un evaporador adecuado. El extracto espeso obtenido en esta etapa se seca, por ejemplo mediante el uso de un horno de secado al vacío o un convertidor de secado al vacío.

Se pueden añadir todos o algunos excipientes durante el secado para facilitar el procedimiento adicional del extracto. Por norma se pueden añadir durante el procedimiento hasta 10 % de uno o más constituyentes.

Preferiblemente se añade una parte del regulador de flujo tal como sílice anhídrica coloidal, al extracto durante o antes de la mezcla con los otros constituyentes. Preferiblemente la composición del extracto resultante contiene de 0,5 a 10 % en peso, en particular 2,5 a 7,5 % en peso, más preferiblemente 4 % en peso de sílice anhídrica coloidal.

Sorprendentemente, los comprimidos obtenidos a partir de un extracto a los cuales se ha añadido una parte de los excipientes durante el procedimiento de secado muestran una estabilidad mejorada.

Lo más preferiblemente el comprimido revestido con una película según la invención consta de

- 300 a 500 mg, preferiblemente 320 a 400 mg, en particular aproximadamente 355 a 380 mg de extracto acuoso seco de hojas de parra roja (4-6:1) (300 to 500 mg, preferably 320 to 400 mg, in particular about 355 to 380 mg of dry aqueous extract of red vine leaf (4-6:1) (*extractum vitis viniferae foliae aequosum siccum*), que puede contener hasta 10 % en peso de regulador de flujo, en particular sílice anhídrica, coloidal;
- los siguientes excipientes del núcleo del comprimido:

celulosa microcristalina, croscarmelosa de sodio, hidrógeno fosfato de calcio (anhidro), sílice coloidal (anhidra), estearato de magnesio, y opcionalmente crospovidona, y

- un comprimido que consta de:

hipromelosa, gliceril triestearato, dióxido de titanio (E 171), talco, óxido férrico, rojo (E 172).

5

Se prepararon los comprimidos revestidos con una película con los ingredientes listados en las siguientes tablas A y B:

Tabla A

| Nombre del ingrediente | Cantidad por comprimido revestido con una película [mg / 658,000 mg] | Función |
|--------------------------------------|--|------------------------------------|
| <u>Núcleo del comprimido</u> | | |
| Vitis viniferae folium | 384,000 | Ingrediente activo |
| Extracto acuoso seco (4-6 :1) | | |
| Celulosa Microcristalina | 219,000 | Aglutinante, desintegrante |
| Croscarmelosa de sodio | 18,000 | Desintegrante |
| Hidrógeno fosfato de calcio, anhidro | 30,000 | Agente de carga |
| sílice anhidra, coloidal | 4,000 | regulador de flujo, desintegración |
| Estearato de Magnesio | 9,000 | acelerador lubricante |
| <u>Película del comprimido</u> | | |
| Hipromelosa | 11,383 | Formador de la película |

| | | |
|-----------------------------|-------|----------------------------|
| Gliceril-triestearato | 1,138 | Plastificante |
| Dióxido de titanio (E 171) | 0,783 | Agente colorante |
| Talco | 3,131 | Agente de
revestimiento |
| Óxido férrico, rojo (E 172) | 1,585 | Agente colorante |

Se mezcla el extracto con los excipientes del núcleo del comprimido y se comprime en una prensa para comprimidos adecuada

| Nombre del ingrediente | Cantidad por
comprimido revestido
con una película
[mg / 658,000 mg] | Función |
|--|---|---|
| <u>Núcleo del comprimido</u> | | |
| Vitis viniferae folium | 380,000 | Ingrediente activo |
| Extracto acuoso seco
(4-6 :1) | | |
| silíce, coloidal,anhidro | 15,000 | Aglutinante |
| Celulosa Microcristalina | 214,000 | Aglutinante,
desintegrante |
| Croscarmelosa de sodio | 18,000 | Desintegrante |
| Hidrógenofosfato de calcio,
anhidro | 30,000 | Agente de carga |
| silíce coloidal, anhidra | 6,000 | regulador de flujo,
desintegración
acelerador |
| Estearato de Magnesio | 9,000 | Lubricante |
| Crospovidona | 18,000 | desintegrante |
| <u>Película del comprimido</u> | | |

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| | | |
|-----------------------------|--------|-------------------------|
| Hipromelosa | 11,383 | Formador de la película |
| Gliceril-triestearato | 1,138 | Plastificante |
| Dióxido de titanio (E 171) | 0,783 | Agente colorante |
| Talco | 3,131 | Agente de revestimiento |
| Óxido férrico, rojo (E 172) | 1,665 | Agente colorante |

Se mezcla el extracto con 15,000 mg de sílica durante el proceso de secado, lo que rinde un extracto que consta de 96 % en peso de los ingredientes del extracto y 4 % de sílice. Esta mezcla resultante se mezcla con los excipientes restantes del núcleo del comprimido y se comprime en una prensa de comprimidos adecuada.

Las fuerzas de compresión que se necesitan para producir comprimidos de resistencia a la rotura adecuada y por tanto con los tiempos de rotura requeridos son dependientes de las formas y tamaños de las herramientas de perforación utilizadas. Se prefieren fuerzas de compresión en el intervalo de 2-20 kN. Fuerzas de compresión mayores pueden llevar a comprimidos con liberación retardada de la sustancia activa. Fuerzas de compresión menores pueden producir comprimidos inestables mecánicamente. Los núcleos de los comprimidos pueden tener diferentes formas, las formas preferidas son formas redondas biplanaras o biconvexas y oblongas.

La solución de revestimiento se prepara mezclando el agente formador de la película con los materiales colorantes y un plastificante en agua. Usando un molde de revestimiento adecuado la solución de revestimiento en forma de película se aplica sobre los núcleos de los comprimidos.

Preferiblemente, los comprimidos tienen una forma oblonga para facilitar la ingestión. En el caso de un comprimido revestido con una película que contiene 300 mg de extracto y una relación de extracto a excipiente como se ha indicado antes, un comprimido oblongo puede ser aproximadamente 17-18 mm de largo y tener una anchura de 8 a 9 mm. Estos comprimidos revestidos con una película de la Tabla A se denominan de aquí en adelante "AS 195".

Para mejorar la circulación sanguínea y/o el suministro de oxígeno de las extremidades inferiores, el comprimido debe tomarse en dosis que se corresponden con 150 a 1000 mg de extracto, preferiblemente 300-800 mg, en particular 350-750 mg, al día. La cantidad total de extracto se puede dividir hasta en 1 a 3 comprimidos

revestidos con una película al día. La dosis diaria se debe tomar de una vez, preferiblemente por la mañana.

Se puede esperar una mejora admirable de los síntomas en 6 semanas de uso continuo. El efecto óptimo se mantiene o amplifica con el uso prolongado.

5 Métodos

Participantes

Se inscribieron pacientes masculinos y femeninos, de 18 años o más, que tienen CVI I o CVI según Widmer, con diagnóstico confirmado y presente durante al menos un año. Deben estar ausentes enfermedades relevantes concomitantes. Los
10 pacientes que tomaron fármacos para aliviar sus síntomas CVI en 4 semanas o que fueron tratados con theophilina, diuréticos, glicósidos cardíacos inhibidores ACE antagonistas del calcio en 8 días antes del primer examen no se permitió que se inscribiesen. Los vendajes de compresión o terapia concomitante para los problemas venosos estuvieron prohibidos durante la participación en la prueba .

15 Planteamiento y procedimientos

Se realizó el estudio cruzado, controlado con placebo, aleatorio, a doble ciego (double-blind) según los principios de la declaración de Helsinki y la International Conference of Harmonisation of Good Clinical Practice.

Cada paciente participó durante 17 semanas en el estudio: durante una
20 semana limpio (tratado con placebo), durante un periodo de tratamiento de seis semanas (Grupo 1 empezó con AS 185, Grupo 2 empezó con placebo), durante cuatro semanas limpio (tratado con placebo), y durante un segundo periodo de tratamiento de seis semanas (Grupo 1 continuó con placebo, Grupo 2 continuó con el AS 185 (comprimidos revestidos con una película que contienen 360 mg de extracto seco de
25 hojas de parra roja) o se tomaron comprimidos de placebo según la pauta de dosificación como una dosis única por la mañana. Ambos comprimidos eran idénticos con respecto al tamaño, forma, peso, apariencia interna, y sabor.

Para la flujometría de láser Doppler el equipo fue proporcionado por LMTB, Berlin, Germany (por ejemplo, Doerschel K, Mueller G. *Velocity resolved laser Doppler flow measurement in skin. Lasermmedizin* 1996;12:163-171.). El equipo es una unidad
30 móvil basada en un ordenador que usa una frecuencia de láser de 785 nm. La sonda del láser se fijó a 3,5 cm de distancia al tobillo interno en la plama más afectada. Después de 30 minutos sentado para adaptarse a la temperatura ambiente, la medida empezó después de 10 minutos de pla (256 puntos de medida, duración aproximada de la medida 0,4 segundos). La luz de fondo desparramada se recuperó mediante dos
35 diodos en el intervalo de frecuencias entre 0,2 a 37,2 kHz. Los datos se procesaron

usando una transformación rápida de Fourier. Finalmente, los datos de salida referidos al intervalo de frecuencias entre 0,2 a 10,0 kHz para los vasos en el plexo venoso reticular (vasos más grandes principalmente termoreguladores, diámetro más de 30 micrómetros) y en el intervalo de frecuencias entre 10,1 a 37,2 kHz para los capilares en el plexo venoso subpapilar (vasos nutritivos superficiales pequeños, diámetro de 6 a 30 micrómetros).

Se midió la presión de oxígeno transcutánea (tcPO₂) usando electrodos polarográficos modificados tipo Clark que contenían cátodos de metales nobles y ánodos de cloruro de plata/plata (TCM 3, Radiometer Copenhagen, Brønshøj, Denmark). Un elemento calefactor adyacente al ánodo mantenía la temperatura de la piel a 43° Celsius. A esta temperatura las arteriolas están máximamente dilatadas, tcPO₂ se aproxima al PO₂ de la sangre arterial (por ejemplo, Bollinger A, Jäger K, Jünger M, Selfert H. *The vascular laboratory: advances in non-invasive techniques*. World J Surg 1988;12:724-731.).

El electrodo se unió a la superficie de la piel mediante un dispositivo en forma de anillo adhesivo que se relleno con solución salina fisiológica, 3,5 cm anteriolateral desde la sonda del láser Doppler. Después de 30 minutos sentado para la adaptación a temperatura ambiente se comenzó la medida después de 10 minutos de pie. La medida duró aproximadamente 15 minutos. Los valores de tcPO₂ se expresan en una columna de milímetros de mercurio (mmHg). Los valores normales disponibles para el dorso de los pies de los pacientes sin CVI están situados en un intervalos entre 40 y 80 mmHg.

Se midió la temperatura local de la piel con un termistor fijado de forma adyacente a un electrodo de oxígeno en la región perimaleolar. Para minimizar los efectos de la perfusión de la piel, las medidas de LDF y tcPO₂ se realizaron entre 28 y 32° C de temperatura local de la piel.

Se midieron las circunferencias del tobillo y de la pantorrilla usando una cinta métrica. Las medidas se llevaron a cabo en el tobillo lateral y medio y hacia la mitad de la pantorrilla.

Los síntomas subjetivos de CVI (piernas pesadas cansadas, sensación de tensión, sensación de hormigueo, y dolor) se midieron usando una escala visual análoga de 10-cm con el cero como "ninguno en absoluto" y 10 cm como "muy fuerte".

La eficacia del tratamiento global fue graduada por los pacientes e investigadores en una escala gradual verbal de 4 puntos (bueno, satisfactorio, no satisfactorio, y malo) al final de cada periodo de tratamiento.

La tolerancia global fue graduada por los pacientes e investigadores en una escala gradual verbal de 4 puntos (bueno, satisfactorio, no satisfactorio, y malo) A los pacientes se les preguntó acerca de su bienestar en términos generales en cada visita.

Resultados

5 Se incluyeron setenta y una mujeres y hombres de edades entre 32 y 76 años con etapas I y II de CVI probadas según Widmer. La edad media ($\pm$ desviación estándar) era $55,2 \pm 7,7$ years; 55 eran mujeres, 16 hombres. El estado flebotológico reveló varicosis de intensidad moderada o severa en 47 (87,1%), pigmentación en 27 (38,6%), edema de tobillo en 28 (37,1%), edema de pierna inferior en 25 (35,7%)
10 pacientes. Estaban presente signos medios de atrofia en 13 pacientes (18,6%), signos de eczema en ninguno (Tabla 1).

Tabla 1: Características demográficas y básicas de CVI

| | AS 195 / Placebo
(n=36) | Placebo / AS195
(n=35) |
|---|----------------------------|---------------------------|
| Variantes continuas (media (Intervalo)) | | |
| Edad [años] | 66 (32-76) | 66 (37-76) |
| Altura [cm] | 168 (150-188) | 165 (150-191) |
| Peso [kg] | 76,5 (48-97) | 73 (55-120) |
| Índice de masa corporal [kg/m ²] | 27,6 (20,6-32,0) | 26,7 (20,1-42,5) |
| Presión sistólica sanguínea [mmHg] | 130 (100-150) | 135 (120-140) |
| Presión diastólica sanguínea [mmHg] | 80 (60-90) | 80 (65-90) |
| Variantes categóricas (n (%)) | | |
| Hembra | 24 (66,7) | 31 (88,6) |
| Fumador habitual | 4 (11,1) | 1 (2,9) |
| Etapas CVI | | |
| etapa I | 26 (72,2) | 23 (65,7) |
| etapa II | 10 (27,8) | 12 (34,3) |
| estado flebotológico de intensidad de moderada a severa | | |
| Varicosis | 26 (72,2) | 22 (62,9) |
| Pigmentación | 11 (30,6) | 17 (48,6) |
| Atrofia | 0 (0,0) | 0 (0,0) |
| Eczema | 0 (0,0) | 0 (0,0) |
| Edema de tobillo | 13 (36,1) | 14 (40,0) |
| Edema de la parte inferior de la pierna | 12 (33,3) | 14 (40,0) |

15

Las violaciones del protocolo no ocurrieron en los restantes pacientes. Por tanto, todos los pacientes se mantuvieron en los análisis de intención de tratar (Figura 1). Las características de los pacientes se distribuyeron homogéneamente entre las dos secuencias de tratamiento (Grupo 1, Grupo 2) excepto en cuanto a la relación de

sexos (12 hombres en el grupo 1, 4 hombres en el grupo 2) (Tabla 1). Los valores de base para los parámetros de láser Doppler, la oximetría transcutánea, las circunferencias del tobillo y de la pantorrilla, y los síntomas subjetivos fueron comparables para el Grupo 1 y el Grupo 2 (Tabla 2). La conformidad con los comprimidos revestidos con una película fue de aproximadamente de 100 % en ambas secuencias de tratamiento.

Tabla 2: Media (±SD) de las características de base de cada periodo de tratamiento

| | Periodo 1 | | Periodo 2 | |
|-----------------------------------|------------------|-------------------|------------------|-------------------|
| | AS 195
(n=36) | Placebo
(n=34) | AS 195
(n=34) | Placebo
(n=36) |
| Flujometría de láser Doppler [AU] | | | | |
| 10-37 kHz | 303,5 (135,2) | 333,5 (153,0) | 275,4 (126,4) | 293,3 (119,9) |
| < 10 kHz | 352,7 (87,7) | 370,8 (120,0) | 174,7 (77,0) | 189,4 (67,6) |
| Oximetría transcutánea [mmHg] | 32,1 (7,0) | 32,3 (6,4) | 30,1 (6,2) | 30,8 (6,4) |
| Circunferencia [cm] | | | | |
| Tobillo | 20,3 (2,2) | 20,4 (2,4) | 20,2 (2,6) | 20,3 (2,2) |
| Pantorrilla | 34,7 (3,1) | 34,2 (3,0) | 34,0 (3,1) | 34,6 (3,2) |
| Síntomas subjetivos [cm] | | | | |
| Piernas cansadas/pesadas | 4,3 (2,8) | 3,7 (2,9) | 4,6 (2,9) | 5,2 (2,6) |
| Dolor en las piernas | 4,0 (3,2) | 3,2 (3,1) | 4,5 (2,7) | 4,9 (3,1) |
| Sensación de tensión | 4,5 (2,9) | 4,1 (2,8) | 4,5 (2,6) | 5,1 (2,5) |
| Sensación de hormigueo | 3,3 (3,1) | 2,7 (2,9) | 3,7 (2,6) | 4,2 (2,8) |

10

Las medidas de flujo de láser Doppler en el intervalo de frecuencias de 10-37 kHz se eligieron como punto final principal. Estas frecuencias se sabe que están determinadas por el número de eritrocitos y sus movimientos (velocidad de flujo) en los capilares de la capa superficial de la piel de la pierna. Después de 6 semanas las frecuencias de láser Doppler (10-37 kHz) aumentaron en el grupo con AS 195 (más 241,8±16,7 AU) pero disminuyeron en el grupo con placebo (menos 41,0±18,7 AU, p<0,0001) (Tabla 3). Este efecto se hizo presente tan pronto como 3 semanas después comenzar el tratamiento (p<0,0001) (Tabla 4, Figura 2).

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Tabla 3: Media ($\pm$ SEM) del cambio de la base ajustado para efectos de periodo, 95 % Intervalo de seguridad para contrastes de tratamiento valor de p después de 3 semanas de tratamiento con 360 mg de AS 195 o placebo

| | Tratamiento | | Diferencia
(n=70) | Contraste de tratamiento | | Valor de
p |
|------------------------------|------------------|-------------------|----------------------|----------------------------------|----------|---------------|
| | AS 195
(n=70) | Placebo
(n=70) | | Intervalo de seguridad
(n=70) | | |
| Semana 3 | | | | | | |
| Flujometría de láser Doppler | | | | | | |
| [AU] | | | | | | |
| 10-37 kHz | 132,2 (11,9) | -28,2 (11,9) | 160,5 | 127,0 to 194,0 | < 0,0001 | |
| < 10 kHz | -3,7 (8,2) | -99,9 (9,2) | 96,2 | 70,2 to 122,2 | < 0,0001 | |
| Oximetría transcutánea | 0,62 (0,97) | -3,84 (0,97) | 4,46 | 1,72 to 7,20 | 0,0018 | |
| [mmHg] | | | | | | |
| Circunferencia [cm] | | | | | | |
| Tobillo | -0,18 (0,09) | 0,21 (0,09) | -0,40 | -0,65 to -0,15 | 0,0025 | |
| Pantorrilla | -0,24 (0,04) | 0,04 (0,04) | -0,28 | -0,40 to -0,17 | < 0,0001 | |
| Subjective symptoms [cm] | | | | | | |
| Piernas | -0,94 (0,25) | 0,21 (0,25) | -0,73 | -1,42 to -0,04 | 0,0398 | |
| cansadas/pesadas | | | | | | |
| Dolor en las piernas | -1,17 (0,23) | -0,24 (0,23) | -0,94 | -1,59 to -0,28 | 0,0061 | |
| Sensación de tensión | -1,00 (0,24) | -0,52 (0,24) | -0,49 | -1,17 to 0,19 | 0,1588 | |
| Sensación de | -0,99 (0,26) | -0,20 (0,26) | -0,79 | -1,52 to -0,06 | 0,0335 | |
| hormigueo | | | | | | |

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Tabla 4: Media (±SEM) del cambio de la base ajustado para efectos de periodo, 95 % intervalo de seguridad para contrastes de tratamiento valor de p después de 6 semanas de tratamiento con 360 mg de AS 195 o placebo

| | Treatment | | Difference
(n=70) | Treatment contrast | |
|-----------------------------------|------------------|-------------------|----------------------|-------------------------------|----------|
| | AS 195
(n=70) | Placebo
(n=70) | | Confidence interval
(n=70) | p value |
| Semana 3 | | | | | |
| Flujometría de láser Doppler [AU] | | | | | |
| 10-37 kHz (punto final principal) | 241,8 (18,7) | -41,0 (18,7) | 282,8 | 229,9 to 335,7 | < 0,0001 |
| < 10 kHz | 57,0 (12,4) | -107,7 (12,4) | 164,7 | 129,7 to 199,7 | < 0,0001 |
| Oximetría transcutánea [mmHg] | 1,35 (0,97) | -7,27 (0,87) | 8,63 | 5,88 to 11,38 | < 0,0001 |
| Circunferencia [cm] | | | | | |
| Tobillo | -0,39 (0,09) | 0,29 (0,09) | -0,68 | -0,94 to -0,43 | < 0,0001 |
| Pantorrilla | -0,54 (0,05) | 0,14 (0,05) | -0,68 | -0,83 to -0,53 | < 0,0001 |
| Subjective symptoms [cm] | | | | | |
| Piernas cansadas/pesadas | -0,78 (0,33) | -0,94 (0,33) | 0,16 | -0,76 to 1,09 | 0,7285 |
| Dolor en las piernas | -0,76 (0,35) | -0,88 (0,35) | 0,10 | -0,88 to 1,09 | 0,8323 |
| Sensación de tensión | -0,96 (0,35) | -1,40 (0,35) | 0,44 | -0,48 to 1,44 | 0,3819 |
| Sensación de hormigueo | -0,55 (0,30) | -0,66 (0,30) | 0,11 | -0,75 to 0,96 | 0,8044 |

90

Se considera que las medidas de flujo de láser Doppler en el intervalo de frecuencias por debajo de 10 kHz están determinadas por el número de eritrocitos y sus movimientos (velocidad de flujo) en los capilares de la capa termoreguladora principal más profunda de la piel de la pierna. Después de 6 semanas las frecuencias de láser Doppler (por debajo de 10 kHz) aumentaron en el grupo con AS 195 (más $57,0 \pm 12,4$ AU) pero disminuyeron en el grupo con placebo (menos $107,7 \pm 12,4$ AU $p < 0,0001$) (Tabla 3). Este efecto parece depender de las condiciones climáticas durante el periodo de tratamiento. Durante el periodo de estudio de temperaturas moderadas (Abril/Mayo) las medidas de láser Doppler (< 10 kHz) permanecieron sin cambios el grupo de tratamiento con AS 195 después de una caída inicial mientras que las medidas en el grupo con placebo disminuyeron ($p < 0,0001$). Durante el periodo de estudio de altas temperaturas (Julio/Agosto) las medidas de láser Doppler (< 10 kHz) aumentaron en el grupo de tratamiento con AS 195 y permanecieron constantes en el grupo con placebo ($p < 0,0001$).

La presión de oxígeno transcutánea aumentó en el grupo con AS 195 (más $1,35 \pm 0,97$ mmHg) pero disminuyó en el grupo con placebo (menos $7,27 \pm 0,97$ mmHg, $p < 0,0001$). Esta observación fue consecuente en ambos periodos de tratamiento y podría estar, por tanto, en línea con el flujo de láser Doppler en la capa superficial nutritiva de la piel (es decir, 10-37 kHz) (Tabla 3.4, Figura 3).

La reducción de la circunferencia del tobillo importante estadísticamente y clínicamente relevante (después de 3 semanas: AS 195 menos $0,19 \pm 0,09$ cm, placebo más $0,21 \pm 0,09$ cm, $p = 0,0025$) y de la pantorrilla (después de 3 semanas: AS 195 menos $0,24 \pm 0,04$ cm, placebo más $0,04 \pm 0,04$ cm, $p < 0,0001$) indican un comienzo de la acción tan pronto como tres semanas después de comenzar el tratamiento (Tabla 3). Este efecto se hace más pronunciado después de 6 semanas (AS 195 tobillo: menos $0,39 \pm 0,09$ cm, pantorrilla: menos $0,54 \pm 0,05$; placebo tobillo: más $0,29 \pm 0,09$ cm, pantorrilla: más $0,14 \pm 0,05$ cm, $p < 0,0001$) (Tabla 4)

No hubo ningún cambio relevante de la intensidad de los síntomas subjetivos en relación a CVI después de 6 semanas de tratamiento. Este resultado está en línea con los de un estudio previo en el que los síntomas subjetivos medidos sobre una escala visual análoga se redujeron sólo después de largos periodos de tratamiento (12 semanas).

Raramente ocurren en este estudio sucesos adversos. Trece de los 71 pacientes experimentaron al menos un suceso adverso, 12 de ellos experimentaron la aparición de la acción mientras estaban en tratamiento con placebo, uno mientras

estaba en tratamiento con AS 195 (bronquitis, intensidad moderada, que se considera por parte del investigador que no está relacionada con el fármaco). El paciente que murió de una parada cardíaca había sido tratado con placebo (nunca recibió AS 195 en esta prueba). Todos los pacientes valoraron la tolerancia global como buena o satisfactoria. Los parámetros de laboratorio no cambiaron durante el estudio.

Discusión

Se ha demostrado en un estudio previo (WO 01/28363) que el extracto de hojas de parra roja AS 195 reduce el edema de la parte inferior de la pierna, la circunferencia de la pantorrilla, y la circunferencia del tobillo además de mejorar los síntomas subjetivos relacionados con la insuficiencia venosa crónica tratados una vez al día durante 12 semanas.⁷ El presente estudio se diseñó para proporcionar información adicional sobre el mecanismo subyacente de acción investigando la microcirculación como un parámetro sustituto relevante clínicamente para CVI en relación con los problemas en las piernas. Este estudio es el primero en pacientes CVI que ayuda a investigar además de la reducción del edema en las piernas, efectos relevantes clínicamente adicionales en relación con la terapia con extracto de hojas de parra roja. El drenaje venoso reducido da como resultado una microcirculación cutánea dañada con alteraciones tróficas de la piel. Si CVI queda sin tratar este estado puede incluso dar lugar a úlceras venosas en las piernas. La flujometría de láser Doppler, como se usa en el presente estudio, es un método válido y los efectos objetivos del tratamiento que pueden estar relacionados con la reducción del volumen experimentada subjetivamente después de 3 meses de tratamiento.

Los resultados del estudio se ajustan con los datos clínicos disponibles para AS 195 y añaden información sobre la aparición de la acción. El volumen de la pierna como un parámetro objetivo se reducirá en un grado clínicamente relevante y estadísticamente importante después de 6 semanas de tratamiento. Este efecto objetivo también se ha publicado recientemente con extracto de semillas de castaña de Indias (por ejemplo, Diehm C, Trampisch HJ, Lange S, Schmidt C. *Comparison of leg compression stocking and oral horse-chestnut seed extract therapy in patients with chronic venous insufficiency. Lancet* 1996;347:292-294.) y Butchers Broom (por ejemplo, Vanscheidt W, Jost V, Wolna P, et al. *Efficacy and safety of a Butcher's Broom preparation (Ruscus aculeatus L. extract) compared to placebo in patients suffering from chronic venous insufficiency. Drug Res* 2002;52(4):243-250.).

En el presente estudio se demostró que los parámetros de la flujometría de láser Doppler, las circunferencias del tobillo y la pantorrilla y la presión de oxígeno transcutánea se vieron afectados tan pronto como después de 3 semanas de

tratamiento. En contraste, los síntomas subjetivos de CVI graduados sobre una escala visual análoga no eran significativamente diferentes del placebo después de 6 semanas de tratamiento a como fueron en el estudio previo. Una duración del tratamiento de 12 semanas es obligatoria para una reducción relevante de los síntomas CVI subjetivos.

Los presentes resultados sugieren un papel principal del extracto de hojas de parra roja en la prevención de la progresión de CVI y en la aparición de lesiones de piel tróficas y pueden incluso prevenir o retrasar la transición desde estados tempranos clínicamente no relevantes de CVI al estado I de CVI.

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REIVINDICACIONES

1. Un comprimido revestido con una película que comprende los siguientes constituyentes:

5 (a) el menos 50 % en peso de un extracto seco de hojas de parra roja, que es obtenible por extracción de hojas de parra roja con agua y secado, y opcionalmente adición de hasta 10 % en peso de sílice en relación con la cantidad total de componente (a);

10 (b) hasta 50 % en peso de un excipiente que consta esencialmente de
- el menos un aglutinante,
- el menos un desintegrante,
- al menos un agente de carga, y
- al menos un lubricante; y

15 (c) una película del comprimido que consta esencialmente de un formador de película, un plastificante, un agente de revestimiento y opcionalmente un agente colorante.

2. Un comprimido revestido con una película según la reivindicación 1, que comprende

20 (a) de 50 a 70 % en peso de dicho extracto seco de hojas de parra roja;
 (b) de 25 a 49 % en peso de dicho excipiente, y
 (c) de 1 a 5 % en peso de dicha película del comprimido,
basado en la masa total del comprimido revestido con una película.

3. Un comprimido revestido con una película según las reivindicaciones 1 ó 2, que comprende

25 (a) de 51 a 59 % en peso de dicho extracto seco de hojas de parra roja;
 (b) de 38 a 48 % en peso de dicho excipiente, y
 (c) de 1 a 3 % en peso de dicha película del comprimido,
basado en la masa total del comprimido revestido con una película.

30 4. Un comprimido revestido con una película según cualquiera de las reivindicaciones precedentes, en el que el extracto acuoso de hojas de parra roja es obtenible por un método que comprende las etapas de:

 (a) recolectar las hojas de parra roja en un momento en el que el contenido de flavonoides haya alcanzado un óptimo;
 (b) secar y prensar las hojas;
35 (c) cortar las hojas en trozos;
 (d) extraer las hojas con agua a elevadas temperaturas durante 6 a 10 horas;

(e) opcionalmente concentrar el extracto obtenido, y

(f) y opcionalmente añadir hasta 10 % en peso de regulador de flujo en relación con la cantidad total de extracto resultante durante el proceso de secado (e).

5 5. Un método según la reivindicación 4, en el que las hojas de la etapa (iv) se extraen con agua a temperaturas de 60 a 80 °C.

6. Un comprimido revestido con una película según cualquiera de las reivindicaciones precedentes, en el que el excipiente (b) consta esencialmente de

- 70 a 85 % en peso de al menos un aglutinante,
- 0,5 a 12,5 % en peso de al menos un desintegrante,
- 10 - 5 a 15 % en peso de al menos un agente de carga, y
- 1 a 5 % en peso de al menos un lubricante,

basado en la masa total de los excipientes (b).

7. Un comprimido revestido con una película según cualquiera de las reivindicaciones precedentes, en el que el aglutinante se selecciona entre celulosa en
15 polvo, celulosa microcristalina, almidón, polivinilpirrolidona, copolímeros de vinilpirrolidona con otros derivados vinílicos, derivados de celulosa y mezclas de estos compuestos.

8. Un comprimido revestido con una película según cualquiera de las reivindicaciones precedentes, en el que el desintegrante se selecciona entre sílica coloidal, glicolato de almidón y sodio, polivinilpirrolidona reticulada (croscapovidona), sal
20 de croscarmelosa de sodio (sal de sodio de carboximetilcelulosa reticulada), carboximetilcelulosa de sodio, el midón de maíz seco y sus mezclas.

9. Un comprimido revestido con una película según cualquiera de las reivindicaciones precedentes, en el que el agente de carga es un fosfato inorgánico o
25 un hidrógenofosfato.

10. Un comprimido revestido con una película según cualquiera de las reivindicaciones precedentes, en el que el agente de carga se selecciona entre dióxido de silicio, talco, ácido esteárico, estearilumarato de sodio, estearato de magnesio y tribehenato de glicerol.

30 11. Un comprimido revestido con una película según cualquiera de las reivindicaciones precedentes, en el que la película del comprimido (c) consta esencialmente de

- 50 a 85 % en peso de al menos un formador de película,
- 5 a 10 % en peso de al menos un plastificante,
- 35 - 10 a 20 % en peso de al menos un agente de revestimiento, y
- 0 a 15 % en peso de al menos un colorante,

basado en la masa total de la película (c) del comprimido.

12. Un procedimiento para preparar un comprimido revestido con una película según una de las reivindicaciones 1 a 11, que comprende las etapas de:

- 5 (A) mezclar el extracto acuoso seco de hojas de parra roja (a) con los excipientes (b), opcionalmente en presencia de un diluyente volátil;
- (B) opcionalmente cribar la mezcla obtenida;
- (C) comprimir la mezcla con una prensa para comprimidos adecuada; y
- (D) revestir el comprimido resultante con una película para comprimidos (c).

10 13. El uso de un comprimido revestido con una película según una de las reivindicaciones 1 a 11, para preparar una composición farmacéutica o dietética para el tratamiento o prevención de la incomodidad, trastorno y/o enfermedad asociados con la hipervolemia venosa crónica y la hipertensión venosa.

14. Un extracto acuoso de hojas de parra roja es obtenible por un método que comprende las etapas de:

- 15 (a) recolectar las hojas de parra roja en un momento en el que el contenido de flavonoides haya alcanzado un óptimo;
- (b) secar y prensar las hojas;
- (c) cortar las hojas en trozos;
- (d) extraer las hojas con agua a elevadas temperaturas durante 6 a 10 horas;
- 20 (e) opcionalmente concentrar el extracto obtenido, y
- (f) añadir hasta 10 % en peso de regulador de flujo en relación con la cantidad total de extracto resultante durante el proceso de secado (e).

15. El extracto acuoso según la reivindicación 14, que comprende de 2,5 a 7,5 % en peso de sílice coloidal, anhidra.

25 16. El extracto acuoso según la reivindicación 15, que comprende aproximadamente 4,0 % en peso de sílice coloidal, anhidra.

30 COLO 09255-841-024-4
PRP/WPCL9255/ID-000328

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RESUMEN

La invención se refiere a un comprimido revestido con una película que comprende los siguientes constituyentes:

5 (a) al menos 50 % en peso de un extracto seco de hojas de parra roja, que es obtenible por extracción de hojas de parra roja con agua y secado,

(b) hasta 50 % en peso de un excipiente que consta esencialmente de

- al menos un aglutinante,

- al menos un desintegrante,

10 - al menos un agente de carga, y

- al menos un lubricante; y

(c) una película del comprimido que consta esencialmente de un formador de película, un plastificante, un agente de revestimiento y opcionalmente un agente colorante.

15 Además la invención se refiere a un extracto acuoso de hojas de parra roja obtenible por un método que comprende las etapas de:

(a) recolectar las hojas de parra roja en un momento en el que el contenido de flavonoides haya alcanzado un óptimo;

(b) secar y prensar las hojas;

20 (c) cortar las hojas en trozos;

(d) extraer las hojas con agua a elevadas temperaturas durante 6 a 10 horas;

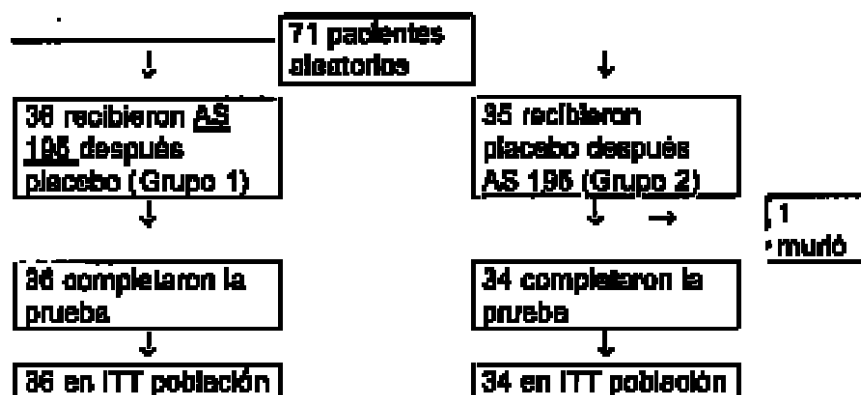
(e) opcionalmente concentrar el extracto obtenido, y

añadir hasta 10 % en peso de regulador de flujo en relación con la cantidad total de extracto resultante durante el proceso de secado (a).

25

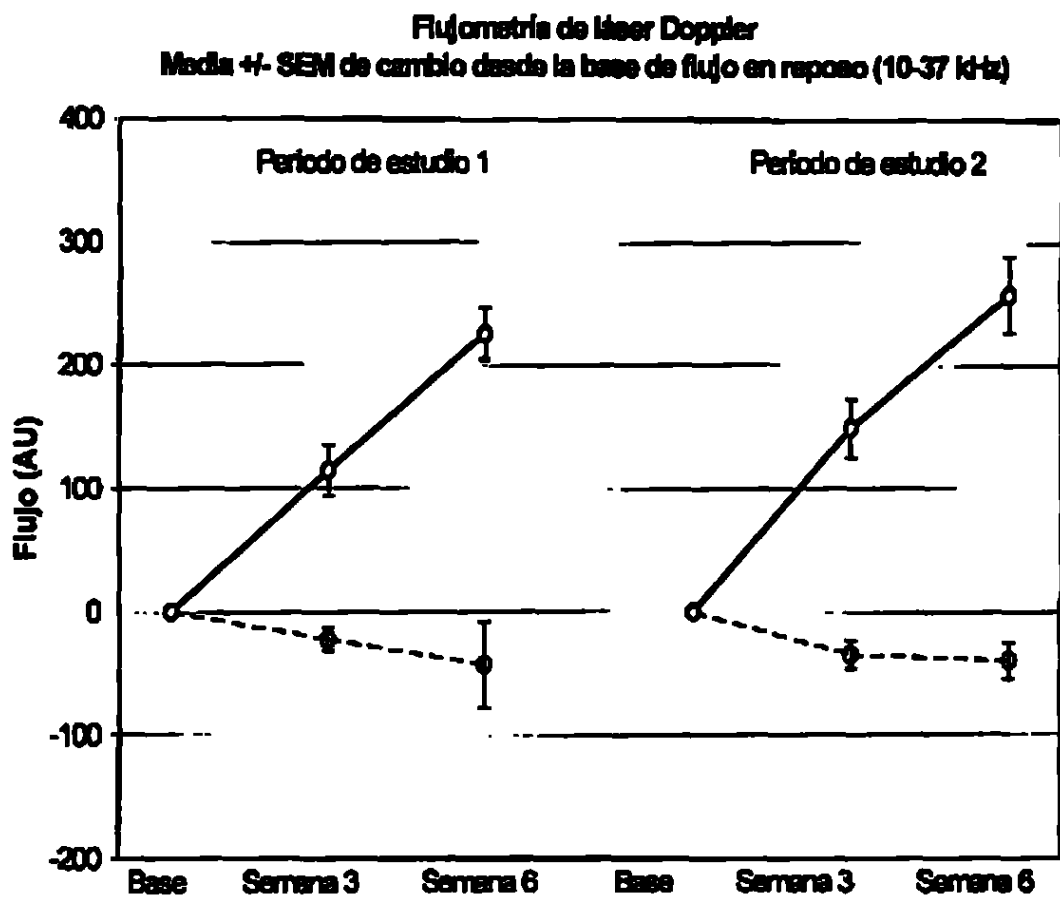
FIGURAS

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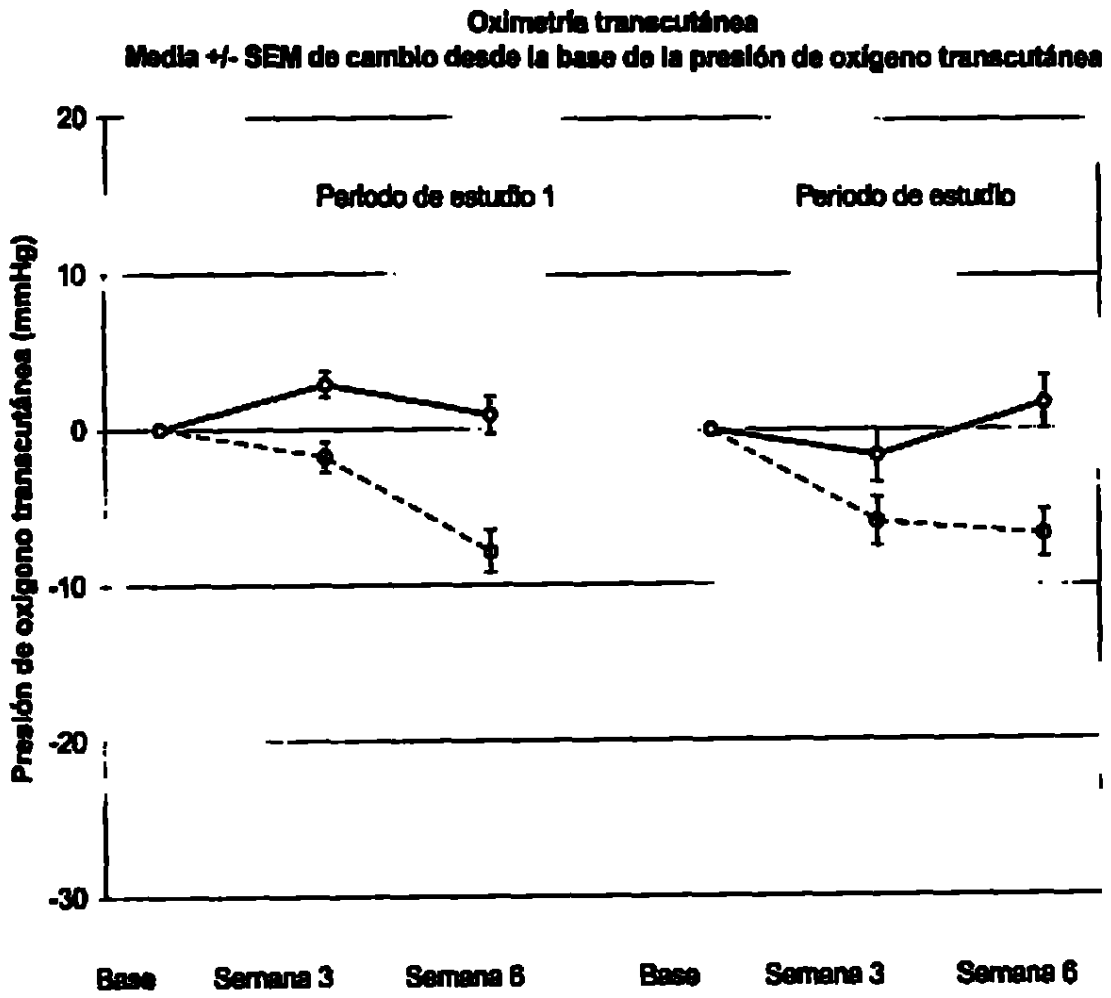
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Fig. 1



5 **Fig. 2**

100



5 **Fig. 3**

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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| REFERENCIA: | Radicación No. | 05 74439 |
| | Solicitud Internacional | PCT/EP2003/014148 |
| | Fecha límite inicio fase Nacional | 31 - 07 - 2005 |
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| | Evento | 379 |
| | Actuación | 416 |
| | Oficio No. | 1117 |
| | Folios | 001 |

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.



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