

	Espacio reservado para el adhesivo de radicación
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DIRECCIÓN DE NUEVAS CREACIONES
Procedimiento acelerado de exámenes de patente (PPH)

1	NÚMERO DE SOLICITUD ANTE LA SIC: NC2017/0003313		
2	GLOBAL - PPH ☐ PAÍS	3	PCT – PPH ☐ PAÍS
4	PROSUR ☐ PAÍS	5	Alianza del Pacífico (AdP) ☐ PAÍS
6	OFICINA DE PRIMERA PRESENTACIÓN (OPP) ☐	7	OFICINA DE EXAMEN ANTERIOR (OEA) ☒
8	NÚMERO DE SOLICITUD O PUBLICACIÓN DE LA SOLICITUD (OPP) ☐ NÚMERO DE SOLICITUD EN OFICINA DE EXAMEN ANTERIOR (OEA): ☒ NÚMERO DE SOLICITUD PCT: ☒		1. PCT/EP2015/074482
9	☐ REPRESENTANTE LEGAL ☒ APODERADO		
APELLIDOS DAZA MONTALVO		NOMBRES CAROLINA	IDENTIFICACIÓN C.C .66.783.790 T.P .141.563
DIRECCIÓN Carrera 11 No. 86-53, piso 3		No. TELÉFONO 6181088	
CIUDAD Bogotá, D.C.		CORREO ELECTRÓNICO notificaciones@clarkemodet.com.co	
PAÍS Colombia		No. RADICACIÓN O PROTOCOLO DE PODER GENERAL	
10	CONDICIONES PARA ACCEDER A ESTE PROCESO:		
10.1. DATOS DE PRIORIDAD ☒ SI ☐ NO			
(33) PAÍS DE ORIGEN 1.EUROPA 2.		CÓDIGO PAÍS EP	(31) NÚMERO 14386034.4 (32) FECHA (AAAA/MM/DD) 2014/12/19
10.2. DATOS SOLICITUD INTERNACIONAL PCT ☒ SI ☐ NO			
Solicitud Internacional No.		PCT/EP2015/074482	Fecha 2015/10/22
Publicación Internacional No.		WO/ 2016/096203	Fecha 2016/06/23
*El solicitante presenta una copia de la(s) reivindicación(es) patentable(s) u otorgable(s) de la solicitud de la Oficina de Primera Presentación que profirió el examen de patentabilidad, junto con una traducción al castellano. ☒ SI ☐ NO *El solicitante presenta los resultados de búsqueda de la Oficina de Examen Anterior, junto con una traducción al castellano ☒ SI ☐ NO			
REQUISITOS PARA EL RECONOCIMIENTO DE LOS RESULTADOS DE EXÁMENES DE PATENTABILIDAD EFECTUADOS A SOLICITUDES EXTRANJERAS Para que la Superintendencia de Industria y Comercio pueda reconocer los resultados de exámenes de patentabilidad producidos por otras Oficinas de Propiedad Industrial se debe cumplir con las siguientes condiciones: (a) Al momento de solicitar el examen de patentabilidad, si el solicitante pide que se reconozcan exámenes de patentabilidad de otras oficinas extranjeras, deberá aportar junto con el pago de la tasa correspondiente, los siguientes anexos: (i) Copia de las resoluciones, fallos o decisiones que han sido relevantes para la determinación de la patentabilidad de la(s) solicitud(es) en la Oficina que haya proferido el examen de patentabilidad que contienen reivindicaciones patentables u otorgables que son la base de la petición, y si es del caso, su traducción al castellano. ☒ SI ☐ NO (ii) Copia de todas las reivindicaciones determinadas como patentables u otorgables en la Oficina que profirió el examen de patentabilidad y, si es del caso, su traducción al castellano. ☒ SI ☐ NO (iii) Copia de los antecedentes, información o documentos citados por el examinador de la Oficina de Primera Presentación del examen de patentabilidad, en las resoluciones, fallos o decisiones correspondientes, incluyendo la literatura no patente. Los documentos de patente deberán presentarse siempre y cuando no estén disponibles para la Superintendencia de Industria y Comercio mediante el simple acceso a bases de datos gratuitas. ☒ SI ☐ NO (iv) Una tabla de correspondencias de las reivindicaciones que han sido determinadas como patentables u otorgables en la solicitud de la Oficina que haya proferido el examen de patentabilidad. ☒ SI ☐ NO			
11	FIRMA DEL SOLICITANTE, DEL APODERADO O DEL REPRESENTANTE LEGAL Junto a cada firma, indicar el nombre del firmante y su calidad (si tal calidad no es obvia al leer el petitorio)		
 CAROLINA DAZA MONTALVO			

10 (iv)	TABLA DE CORRESPONDENCIA DE REIVINDICACIONES		
Reivindicaciones en la solicitud en Colombia (Como se presentaron en respuesta al Oficio de Forma)		Reivindicaciones otorgables en la solicitud internacional	Explicación sobre la suficiente correspondencia ó Comentarios que explican la correspondencia
1. <i>Un proceso para la preparación de un complejo de hie-rro (III) con caseína N-acetil-L-aspartilada, el cual comprende las etapas de</i> <i>(a) reacción de la caseína con cloruro de N-acetil-L-aspartilo, para formar caseína N-acetil-L-aspartilada, en donde primero caseína se disuelve en agua a un pH entre 8 y 9, y reacciona con cloruro de N-acetil-L-aspartilo a una temperatura en el rango de 15°C a 40°C;</i> <i>(b) una reacción posterior de la caseína N-acetil-L-aspartilada con cloruro férrico, en donde una solu-ción acuosa de cloruro férrico se adiciona a una so-lución de caseína N-acetil-L-aspartilada obtenida en la etapa (a) hasta que se alcanza un pH de entre 2,5 y 3, seguido por una recuperación de caseína ferro-N-acetil-L-aspartilada como fase insoluble; y</i> <i>(c) obtener el complejo de hierro (III) con la caseí-na N-acetil-L-aspartilada, en donde la caseína ferro-N-acetil-L-aspartilada es precipitada, filtrada y desacada.</i>		1. <i>Un proceso para la preparación de un complejo de hierro (III) con caseína N-acetil-L-aspartilada, el cual comprende las etapas de</i> <i>(a) reacción de la caseína con cloruro de N-acetil-L-aspartilo, para formar caseína N-acetil-L-aspartilada,</i> <i>(b) una reacción posterior de la caseína N-acetil-L-aspartilada con cloruro férrico; y</i> <i>(c) obtener el complejo de hierro (III) con la caseína N-acetil-L-aspartilada.</i>	En el caso de la reivindicación de la solicitud en Colombia, el contenido fue modificado para incluir condiciones técnicas adicionales, restringiendo su alcance respecto a la presentada originalmente con la PCT. Son en esencia reivindicaciones correspondientes porque en Colombia el alcance está más restringido.
2. <i>El proceso de acuerdo con la reivindicación 1, en donde la caseína utilizada es caseína de grado ali-menticio.</i>		2. <i>El proceso de acuerdo con la reivindicación 1, en donde la caseína utilizada es caseína de grado alimenticio.</i>	Son la misma reivindicación.
3. <i>El proceso de acuerdo con la reivindicación 1, en donde en la etapa (a) el valor de pH durante la reac-ción de cloruro de N-acetil-L-aspartilo con lasolu-ción de caseína es mantenida a un pH de entre 8 y 9.</i>		3. <i>El proceso de acuerdo con la reivindicación 1, en donde la etapa (a) comprende proporcionar una solución de caseína, y en donde la adición de cloruro de N-acetil-L-aspartilo a la solución de caseína es realizada a un pH de entre 6 y 9.</i>	En el caso de la reivindicación de la solicitud en Colombia, el contenido fue modificado para que resultara más clara. Se modificó igualmente el valor de pH. Son en esencia reivindicaciones correspondientes porque en Colombia el alcance está más restringido (depende de la reivindicación 1 que fue restringida).

4. El proceso de acuerdo con la reivindicación 1, en donde el cloruro de N-acetil-L-aspartilo es preparado in situ, de modo preferible a través del uso de reactivos clorantes seleccionados a partir del grupo que consiste de cloruro de tionilo (SOCl ₂), pentacloruro de fósforo (PCl ₅), tricloruro de fósforo (PCl ₃), tetracloruro de carbono (CCl ₄), cloruro de oxalilo (COCl) ₂ , cloruro de fosforilo (POCl ₃), 2-cloro-1,3-bis(metoxicarbonil)guanidina (Palau'Chlor), cloruro cianúrico y N-clorosuccinimida.	4. El proceso de acuerdo con la reivindicación 1, en donde el cloruro de N-acetil-L-aspartilo es preparado in situ, de modo preferible a través del uso de reactivos clorantes seleccionados a partir del grupo que consiste de cloruro de tionilo (SOCl ₂), pentacloruro de fósforo (PCl ₅), tricloruro de fósforo (PCl ₃), tetracloruro de carbono (CCl ₄), cloruro de oxalilo (COCl) ₂ , cloruro de fosforilo (POCl ₃), 2-cloro-1,3-bis(metoxicarbonil)guanidina (Palau'Chlor), cloruro cianúrico y N-clorosuccinimida.	Son la misma reivindicación.
5. El proceso de acuerdo con la reivindicación 1, en donde el complejo de hierro (III) con la caseína N-acetil-L-aspartilada obtenida en la etapa (c) es clarificado antes de ser colocado en desecación o secado por atomizador o secado por congelación.	5. El proceso de acuerdo con la reivindicación 1, en donde el complejo de hierro (III) con la caseína N-acetil-L-aspartilada obtenida en la etapa (c) es clarificado antes de ser colocado en desecación o secado por atomizador o secado por congelación.	Son la misma reivindicación.
6. Un proceso para la preparación de una composición farmacéutica que comprende un complejo de hierro (III) con caseína N-acetil-L-aspartilada de grado alimenticio, en donde dicho proceso comprende el proceso de acuerdo con cualquiera de las reivindicaciones 1 a 5 y la combinación de dicho complejo de hierro (III) con caseína N-acetil-L-aspartilada de grado alimenticio con excipientes farmacéuticos, en particular seleccionados a partir de diluyentes y conservantes.	6. Un proceso para la preparación de una composición farmacéutica que comprende un complejo de hierro (III) con caseína N-acetil-L-aspartilada de grado alimenticio, en donde dicho proceso comprende el proceso de acuerdo con cualquiera de las reivindicaciones 1 a 5 y la combinación de dicho complejo de hierro (III) con caseína N-acetil-L-aspartilada de grado alimenticio con excipientes farmacéuticos, en particular seleccionados a partir de diluyentes y conservantes.	Son la misma reivindicación.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2015/074482

International filing date (day/month/year)
22.10.2015

Priority date (day/month/year)
19.12.2014

International Patent Classification (IPC) or both national classification and IPC
INV. C07K14/47

Applicant
TSETI, Ioulia

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0
Fax: +49 89 2399 - 4465

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Bassias, Ioannis

Telephone No. +49 89 2399-0



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2015/074482

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
 - a. ☐ forming part of the international application as filed:
 - ☐ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2015/074482

Box No. V Reasoned statement under Rule 43b/s.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-6</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-6</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-6</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Item V

- 1 The present application relates to a process for the preparation of iron (III) complex with N-acetyl-L-aspartylated casein (Fe-ASP), comprising the steps of
 - (a) reaction of casein with N-acetyl-L-aspartyl chloride, to form N-acetyl-L-aspartylated casein,
 - (b) subsequent reaction of the N-acetyl- L-aspartylated casein with ferric chloride; and
 - (c) obtaining the iron (III) complex with N-acetyl-L-aspartylated caseinand to the use of complex in a process for preparing a pharmaceutical composition.
- 2 Reference is made to the following documents:
 - D1 WO 2006/021843 A1 (BIOFER S P A [IT]; LAPINI SACCHETTI ALESSANDRO [IT]) 2 March 2006 (2006-03-02)cited in the application
 - D2 EP 0 243 322 B1 (MAGIS FARMACEUTICI [IT]) 29 January 1992 (1992-01-29)cited in the application
 - D3 LAZZARI FLAVIO ET AL: "Overview of clinical trials in the treatment of iron deficiency with iron-acetyl-aspartylated casein", CLINICAL DRUG INVESTIGATION, vol. 25, no. 11, 2005, pages 679-689, XP009182971, ISSN: 1173-2563 cited in the application
- 3 The Fe-ASP which is produced with the process as claimed in the present application is already known in the prior art. D1-D3 disclose Fe-ASP. However, D1 and D2 used a different process for the preparation of Fe-ASP. From D3 it cannot be derived how the Fe-ASP which was used for clinical trials, was produced.

D1 and D2 used a N-acetyl aspartic anhydride for the reaction with casein, whereas in the process of the present application N-acetyl-L-aspartyl chloride is put together with casein. Consequently, the process as described in claims 1-5 is novel over the prior art (Article 33(2) PCT).

The process of claim 6 comprises the process as defined in claims 1-5 and meets therefore also the requirements of Article 33(2) PCT.

It appears that N-acetyl aspartic anhydride is relative expensive for industrial use and also unstable against humidity on storage. Furthermore there is a risk for partial racemization of N-acetyl aspartic anhydride. A process which uses an alternative molecule for the reaction with casein, e.g. N-acetyl-L-aspartyl chloride is therefore superior over a process in which the corresponding anhydride is used, since it is more efficient, due to less enantiomeric impurities in the reaction and additionally is also cheaper.

Consequently, claims 1-5 and 6 meet also the requirements of Article 33(3) PCT.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 30A-131 102	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/EP2015/074482	International filing date (<i>day/month/year</i>) 22 October 2015 (22-10-2015)	(Earliest) Priority Date (<i>day/month/year</i>) 19 December 2014 (19-12-2014)
Applicant TSETI, Ioulia		

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 4 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
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box No. II)

3. ☐ **Unity of invention is lacking** (see Box No III)

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:

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, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. _____
☐ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
b. ☐ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2015/074482

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07K14/47

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, COMPENDEX, EMBASE, FSTA, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2006/021843 A1 (BIOFER S P A [IT]; LAPINI SACCHETTI ALESSANDRO [IT]) 2 March 2006 (2006-03-02) cited in the application the whole document, in particular p. 4, Example 2 and claims 6-10	1-6
A	EP 0 243 322 B1 (MAGIS FARMACEUTICI [IT]) 29 January 1992 (1992-01-29) cited in the application the whole document, in particular the claims ----- -/--	1-6

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents :

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

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

24 November 2015

Date of mailing of the international search report

12/01/2016

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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Fax: (+31-70) 340-3016

Authorized officer

Bassias, Ioannis

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/074482

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LAZZARI FLAVIO ET AL: "Overview of clinical trials in the treatment of iron deficiency with iron-acetyl-aspartylated casein", CLINICAL DRUG INVESTIGATION, vol. 25, no. 11, 2005, pages 679-689, XP009182971, ISSN: 1173-2563 cited in the application the whole document -----	1-6
A	BURON ET AL: "On the racemisation of aspartic anhydride during its preparation", TETRAHEDRON ASYMMETRY, PERGAMON PRESS LTD, OXFORD, GB, vol. 18, no. 13, 17 July 2007 (2007-07-17) , pages 1625-1627, XP022181932, ISSN: 0957-4166, DOI: 10.1016/J.TETASY.2007.07.003 cited in the application -----	1-6

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2015/074482

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006021843 A1	02-03-2006	AT 416193 T EP 1776382 A1 ES 2317270 T3 WO 2006021843 A1	15-12-2008 25-04-2007 16-04-2009 02-03-2006
EP 0243322 B1	29-01-1992	DE 3776388 D1 EP 0243322 A2 ES 2035102 T3 IT 1207996 B	12-03-1992 28-10-1987 16-04-1993 01-06-1989

TRATADO DE COOPERACIÓN DE PATENTES

De la
AUTORIDAD DE BÚSQUEDA INTERNACIONAL

A:

Ver formulario PCT/ISA/220

PCT

OPINIÓN ESCRITA DE LA AUTORIDAD DE
BÚSQUEDA INTERNACIONAL

(Regla 43bis.1 del PCT)

Fecha de envío
(día/mes/año) ver formulario PCT/ISA/210 (segunda hoja)

Referencia del expediente del solicitante o agente
Ver formulario PCT/ISA/220

PARA ACCIÓN ADICIONAL
Ver parágrafo 2 a continuación

Solicitud Internacional No.
PCT/EP2015/0744482

Fecha de presentación internacional
(día/mes/año)
22.10.2015

Fecha de prioridad (día/mes/año)
19.12.2014

Clasificación Internacional de Patente (CIP) o clasificación nacional y CIP

INV. C07K14/47

Solicitante TSETI, Ioulia

1. Esta opinión contiene indicaciones relacionadas con los siguientes ítems:

- | | |
|--|---|
| ☒ Recuadro No. I | Base del informe |
| ☐ Recuadro No. II | Prioridad |
| ☐ Recuadro No. III | No formulación de opinión sobre la novedad, la actividad inventiva y la aplicación industrial |
| ☐ Recuadro No. IV | Falta de unidad de invención |
| ☒ Recuadro No. V | Declaración motivada según la Regla 43bis.1(a)(i) con relación a la novedad, actividad inventiva o la aplicación industrial; citas y explicaciones que soportan dicha declaración |
| ☐ Recuadro No. VI | Ciertos documentos citados |
| ☐ Recuadro No. VII | Ciertos defectos en la solicitud internacional |
| ☐ Recuadro No. VIII | Ciertas observaciones en la solicitud internacional |

2. ACCIÓN POSTERIOR

Si se hace una petición de examen preliminar internacional, esta opinión se considerará como una opinión escrita de la Administración del examen preliminar internacional ("IPEA") salvo en aquellos casos en los que el solicitante elija una Administración distinta a ésta, y la IPEA elegida haya notificado a la Oficina Internacional bajo la Regla 66.1bis(b) que las opiniones escritas de esta Administración de búsqueda internacional no serán consideradas como tales.

Si esta opinión es, como se indica anteriormente, considerada como una opinión escrita de la IPEA, se invita al solicitante a que presente ante la IPEA una respuesta por escrito junto con modificaciones, en su caso, antes de la expiración del plazo de 3 meses a contar desde la fecha de envío del formulario PCT/ISA/220 o antes de la expiración del plazo de 22 meses a contar desde la fecha de prioridad, aplicándose el plazo que expire más tarde.

Para otras opciones, ver el Formulario PCT/ISA/220.

Nombre y dirección de envío de la ISA

Oficina Europea de Patentes
D-80298 Múnich
Tel. +49 89 2399 – 0
Fax: +49 89 2399 – 4465

Fecha de terminación de esta opinión

Ver formulario PCT/ISA/210

Oficial autorizado:

Bassias, Ioannis

Teléfono No. +49 89 2399 - 0

**OPINIÓN ESCRITA DE LA AUTORIDAD
DE BÚSQUEDA INTERNACIONAL**

Solicitud Internacional No.
PCT/EP2015/074482

Recuadro No. 1 Base de esta opinión

1. Con relación al **idioma**, esta opinión ha sido establecida sobre la base de:
☒ la solicitud internacional en el idioma en el cual se presentó
☐ una traducción de la solicitud internacional en _____, el cual es el idioma de una traducción suministrada para los fines de la búsqueda internacional (Reglas 12.3(a) y 23.1(b)).
2. ☐ Esta opinión se ha establecido teniendo en cuenta la **rectificación de un error evidente** autorizado por o notificado a esta Autoridad bajo la Regla 91 (Regla 43bis.1(a))
3. Con relación a cualquier **secuencia de nucleótidos y/o aminoácidos** divulgada en la solicitud internacional, esta opinión ha establecido sobre la base de un listado de secuencia:
 - a. ☐ forma parte de la solicitud internacional como se presentó:
☐ en la forma de un archivo de texto Anexo C/ST .25
☐ en papel o en la forma de un archivo de imagen
 - b. ☐ presentado junto con la solicitud internacional bajo la Regla 13ter.1(a) del PCT para el propósito de la búsqueda internacional únicamente en la forma de un archivo de texto Anexo C/ST .25.
 - c. ☐ presentado posterior a la fecha de presentación internacional para el propósito de la búsqueda internacional únicamente:
☐ en la forma de un archivo de texto Anexo C/ST .25 (Regla 13ter.1(a))
☐ en papel o en la forma de un archivo de imagen (Regla 13ter.1(b) e Instrucciones Administrativas, Sección 713).
4. ☐ Adicionalmente, en el caso que más de una versión o copia de un listado de secuencias ha sido presentado o suministrado, las declaraciones requeridas que la información en las copias subsecuentes o adicionales son idénticas a la de la solicitud como se presentó o no va más allá de la solicitud como se presentó, fueron suministradas.
5. Comentarios adicionales:

**OPINIÓN ESCRITA DE LA AUTORIDAD
DE BÚSQUEDA INTERNACIONAL**

Solicitud Internacional No.
PCT/EP2015/074482

Recuadro No. V Declaración motivada según la Regla 43bis.1(a)(i) con relación a la novedad, nivel inventivo o la aplicación industrial; citas y explicaciones que soportan dicha declaración

1. Declaración

Novedad (N)	Sí: Reivindicaciones	<u>1-6</u>
	No: Reivindicaciones	

Nivel Inventivo (NI)	Sí: Reivindicaciones	<u>1-6</u>
	No: Reivindicaciones	

Aplicación Industrial (AI)	Sí: Reivindicaciones	<u>1-6</u>
	No: Reivindicaciones	

2. Citaciones y explicaciones:

Ver hoja separada

Punto V

- 1 La presente solicitud se relaciona con un proceso para la preparación de complejo de hierro (III) con caseína de N-acetil-L-aspartilado (Fe-ASP), que comprende los pasos de
 - (a) reacción de caseína con cloruro de N-acetilo-L-aspartilado, para formar caseína de N-acetilo-L-aspartilado,
 - (b) posterior reacción de la caseína de N-acetilo-L-aspartilado con cloruro férrico; y
 - (c) obtener el complejo de hierro (III) con caseína de N-acetilo-L-aspartiladoy al uso del complejo en un proceso para preparar una composición farmacéutica.
- 2 Se hace referencia a los siguientes documentos:

D1 WO 2006/021843 A1 (BIOFER S P A [IT]; LAPINI SACCHETTI ALESSANDRO [IT]) 2 de marzo de 2006 (2006-03-02) citado en la solicitud

D2 EP 0 243 322 B1 (MAGIS FARMACEUTICI [IT]) 29 de enero de 1992 (1992-01-29) citado en la solicitud

D3 LAZZARI FLAVIO Y OTROS: "Revisión de ensayos clínicos en el tratamiento de deficiencia de hierro con caseína de hierro-acetil-aspartilado", INVESTIGACION DE DROGA CLINICA, Vol. 25, No. 11, 2005, páginas 679-689, XP009182971, ISSN: 1173-2563, citado en la solicitud
- 3 El Fe-ASP el cual es producido con el proceso como se reivindica en la presente solicitud ya es conocido en el arte previo. D1-D3 divulgan Fe-ASP. Sin embargo, D1 y D2 utilizaron un proceso diferente para la preparación de Fe-ASP. A partir de D3 no se puede derivar cómo se produjo el Fe-ASP que fue utilizado para ensayos clínicos.

D1 y D2 usaron un anhidro aspártico de N-acetilo para la reacción con caseína, mientras que en el proceso de la presente solicitud cloruro de N-acetil-L-aspartilado se pone junto con caseína. En consecuencia, el proceso como se describe en las reivindicaciones 1-5 es novedoso sobre el arte previo (Artículo 33(2) del PCT).

El proceso de la reivindicación 6 comprende el proceso como se define en las reivindicaciones 1-5 y por lo tanto también cumple con los requerimientos del Artículo 33(2) del PCT.

Parece que el anhidro aspártico de N-acetilo es relativamente costoso para uso industrial y también inestable contra humedad en almacenamiento. Además, hay un riesgo para racemización parcial del anhidro aspártico de N-acetilo. Un proceso que utilice una molécula alterna para la reacción con caseína, por ejemplo cloruro de N-acetilo-L-aspartilado es por lo tanto superior sobre un proceso en el cual se utiliza el correspondiente anhidro, dado que es más eficiente, debido a menos impurezas enantioméricas en la reacción y adicionalmente es también más económico.

En consecuencia, las reivindicaciones 1-5 y 6 también cumplen con los requerimientos del Artículo 33(3) del PCT.

TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES

PCT

INFORME DE BÚSQUEDA INTERNACIONAL

(Artículo 18 y Reglas 43 y 44 del PCT)

Referencia del expediente del solicitante o del mandatario 30A-131 102	PARA CONTINUAR LA TRAMITACIÓN	Ver Formulario PCT/ISA/220 y, en su caso, el punto 5 de esta hoja
Solicitud internacional N° PCT/EP2015/074482	Fecha de presentación internacional (día/mes/año) 22 de octubre de 2015 (22-10-2015)	Fecha de prioridad (la más antigua) (día/mes/año) 19 de diciembre de 2014 (19-12-2014)
Solicitante TSETI, Ioulia		

El presente informe de búsqueda internacional, elaborado por esta Administración encargada de la búsqueda internacional, se transmite al solicitante, conforme al Artículo 18. Se remite una copia del mismo a la Oficina Internacional.

Este informe de búsqueda internacional comprende un total de 4 hojas.

☒ Se adjunta una copia de cada uno de los documentos del estado de la técnica citados en el informe.

1. Base del informe

a. En lo que se refiere al **idioma**, la búsqueda internacional se ha realizado sobre la base de:

- ☒ la solicitud internacional en el idioma en el que se presentó
☐ una traducción de la solicitud internacional a _____, que es el idioma de la traducción proporcionada a los fines de la búsqueda internacional (Reglas 12.3.a) y 23.1.b))

b. ☐ Este informe de búsqueda internacional se ha realizado teniendo en cuenta la **rectificación de un error evidente** autorizado por o notificado a esta Administración según la Regla 91 (Regla 43.6bis. a)).

c. ☐ En lo que se refiere a **las secuencias de nucleótidos y/o de aminoácidos** divulgadas en la solicitud internacional, véase Recuadro I.

2. ☐ **Se estima que algunas reivindicaciones no pueden ser objeto de búsqueda** (ver Recuadro II).

3. ☒ **Falta unidad de invención** (ver Recuadro III).

4. Con respecto al **título**,

- ☒ el texto se aprueba según fue remitido por el solicitante.
☐ el texto ha sido establecido por esta Administración con la siguiente redacción:

5. Con respecto al **resumen**,

- ☒ el texto se aprueba según fue remitido por el solicitante.
☐ el texto (reproducido en el Recuadro IV) ha sido establecido por esta Administración de conformidad con la Regla 38.2. El solicitante puede presentar observaciones a esta Administración en el plazo de un mes a contar desde la fecha de expedición del presente informe de búsqueda internacional

6. Con respecto a los **dibujos**,

- a. la figura de los **dibujos** a publicar junto con el resumen es la Figura N°
☐ propuesta por el solicitante.
☐ propuesta por esta Administración, por no haber propuesto el solicitante ninguna figura.
☐ propuesta por esta Administración, por caracterizar mejor, esta figura, la invención.
b. ☐ no debe publicarse ninguna figura.

INFORME DE BÚSQUEDA INTERNACIONAL

Solicitud internacional N°

PCT/EP2015/074482

A. CLASIFICACIÓN DEL OBJETO DE LA SOLICITUD

INV. C07K14/47

ADD.

De acuerdo con la Clasificación Internacional de Patentes (CIP) o según la clasificación nacional y CIP.

B. SECTORES COMPRENDIDOS POR LA BÚSQUEDA

Documentación mínima buscada (sistema de clasificación seguido de los símbolos de clasificación)

C07K

Otra documentación consultada, además de la documentación mínima, en la medida en que tales documentos formen parte de los sectores comprendidos por la búsqueda

Bases de datos electrónicas consultadas durante la búsqueda internacional (nombre de la base de datos y, si es posible, términos de búsqueda utilizados)

EPO-Interno, COMPENDEX, EMBASE, FSTA, Datos WPI, BIOSIS

C. DOCUMENTOS CONSIDERADOS RELEVANTES

Categoría*	Documentos citados, con indicación, si procede, de las partes relevantes	Relevante para las reivindicaciones N°
A	WO 2006/021843 A1 (BIOFER S P A [IT]; LAPINI SACCHETTI ALESSANDRO [IT]) 2 de marzo de 2006 (2006-03-02) citado en la solicitud todo el documento, en particular p.4, Ejemplo 2 y reivindicaciones 6-10 -----	1-6
A	EP 0 243 311 B1 (MAGIS FARMACEUTICI [IT]) 29 de enero de 1992 (1992-01-29) citado en la solicitud todo el documento, en particular las reivindicaciones -----	1-6

☒ En la continuación del Recuadro C se relacionan otros documentos☒ Los documentos de familias de patentes se indican en el Anexo

* Categorías especiales de documentos citados:

“A” documento que define el estado general de la técnica no considerado como particularmente relevante.

“E” solicitud de patente o patente anterior pero publicada en la fecha de presentación internacional o en fecha posterior.

“L” documento que puede plantear dudas sobre una reivindicación de prioridad o que se cita para determinar la fecha de publicación de otra cita o por una razón especial (como la indicada).

“O” documento que se refiere a una divulgación oral, a una utilización, a una exposición o a cualquier otro medio.

“P” documento publicado antes de la fecha de presentación internacional pero con posterioridad a la fecha de prioridad reivindicada.

“T” documento ulterior publicado con posterioridad a la fecha de presentación internacional o de prioridad que no pertenece al estado de la técnica pertinente pero que se cita por permitir la comprensión del principio o teoría que constituye la base de la invención.

“X” documento particularmente relevante; la invención reivindicada no puede considerarse nueva o que implique una actividad inventiva por referencia al documento aisladamente considerado.

“Y” documento particularmente relevante; la invención reivindicada no puede considerarse que implique una actividad inventiva cuando el documento se asocia a otro u otros documentos de la misma naturaleza, cuya combinación resulta evidente para un experto en la materia.

“&” documento que forma parte de la misma familia de patentes.

Fecha en que se ha concluido efectivamente la búsqueda internacional.

Fecha de expedición del informe de búsqueda internacional

24 de Noviembre de 2015

12/01/2016

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Funcionario autorizado

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INFORME DE BÚSQUEDA INTERNACIONAL

Solicitud internacional N°

PCT/EP2015/074482

C. (continuación) DOCUMENTOS CONSIDERADOS RELEVANTES

Categoría*	Documentos citados, con indicación, si procede, de las partes relevantes	Relevante para las reivindicaciones N°
A	LAZZARI FLAVIO Y OTROS: "Revisión de ensayos clínicos en el tratamiento de deficiencia de hierro con caseína de hierro-acetilo-aspartilado", INVESTIGACIÓN DE DROGA CLÍNICA Vol. 25, No. 11, 2005, páginas 679-689, XP009182971 ISSN: 1173-2563 citado en la solicitud todo el documento -----	1-6
A	BURON Y OTROS: "Sobre la racemización de anhídrido aspártico durante su preparación", ASIMETRIA DE TETRAHEDRON, PERGAMON PRESS LTD, OXFORD, GB, Vol. 18, No. 13, 17 de julio de 2007 (2007-07-17) Páginas 1625-1627, XP022181932, ISSN: 0957-4166, DOI: 10.1016/J.TETASY.2007.07.003 citado en la solicitud -----	1-6

INFORME DE BÚSQUEDA INTERNACIONAL

Solicitud internacional N°

PCT/EP2015/074482

Documento de patente citado en el reporte de búsqueda	Fecha de publicación	Miembro de la familia de patentes		Fecha de publicación
WO 2006021843 A1	02-03-2006	AT	416193 T	15-12-2008
		EP	1776382 A1	25-04-2007
		ES	2317270 T3	16-04-2009
		WO	2006021843 A1	02-03-2006
EP 0243322 B1	29-01-1992	DE	3776388 D1	12-03-1992
		EP	0243322 A2	28-10-1987
		ES	2035102 T3	16-04-1993
		IT	1207996 B	01-06-1989

Claims

- 5 1. Process for the preparation of iron (III) complex with N-acetyl-L-aspartylated casein, comprising the steps of
(a) reaction of casein with N-acetyl-L-aspartyl chloride, to form N-acetyl-L-aspartylated casein,
(b) subsequent reaction of the N-acetyl-L-aspartylated casein with ferric chloride;
10 and
(c) obtaining the iron (III) complex with N-acetyl-L-aspartylated casein.
2. The process of claim 1, wherein the casein utilized is food-grade casein.
- 15 3. The process of claim 1, wherein step (a) comprises providing a solution of casein, and wherein addition of N-acetyl-L-aspartyl chloride to the casein solution is performed at a pH of between 6 and 9.
- 20 4. The process of claim 1, wherein the N-acetyl-L-aspartyl chloride is prepared *in situ*, preferably by using chlorinating reagents selected from the group consisting of thionyl chloride (SOCl₂), phosphorus pentachloride (PCl₅), phosphorus trichloride (PCl₃), carbon tetrachloride (CCl₄), oxalyl chloride (COCl)₂, phosphoryl chloride (POCl₃), 2-chloro-1,3-bis(methoxycarbonyl)guanidine (Palau'Chlor), cyanuric chloride and N-chlorosuccinimide.
- 25 5. The process of claim 1, wherein the iron (III) complex with N-acetyl-L-aspartylated casein obtained in step (c) is clarified before being sent on for desiccation or spray-drying or freeze-drying.
- 30 6. A process for preparing a pharmaceutical composition comprising an iron (III) complex with N-acetyl-L-aspartylated food-grade casein, said process comprising the process according to anyone of claims 1-5 and combining said iron (III) complex with N-acetyl-L-aspartylated food-grade casein with pharmaceutical ex-
35 cipients, in particular selected from diluents and preservatives.

Traducción de las Reivindicaciones Originales PCT

consideradas como patentables por la OEA

1. Un proceso para la preparación de un complejo de hierro (III) con caseína N-acetil-L-aspartilada, el cual comprende las etapas de
 - (a) reacción de la caseína con cloruro de N-acetil-L-aspartilo, para formar caseína N-acetil-L-aspartilada,
 - (b) una reacción posterior de la caseína N-acetil-L-aspartilada con cloruro férrico; y
 - (c) obtener el complejo de hierro (III) con la caseína N-acetil-L-aspartilada.
2. El proceso de acuerdo con la reivindicación 1, en donde la caseína utilizada es caseína de grado alimenticio.
3. El proceso de acuerdo con la reivindicación 1, en donde la etapa (a) comprende proporcionar una solución de caseína, y en donde la adición de cloruro de N-acetil-L-aspartilo a la solución de caseína es realizada a un pH de entre 6 y 9.
4. El proceso de acuerdo con la reivindicación 1, en donde el cloruro de N-acetil-L-aspartilo es preparado *in situ*,

de modo preferible a través del uso de reactivos clorantes seleccionados a partir del grupo que consiste de cloruro de tionilo (SOCl_2), pentacloruro de fósforo (PCl_5), tricloruro de fósforo (PCl_3), tetraccloruro de carbono (CCl_4), cloruro de oxalilo (COCl_2), cloruro de fosforilo (POCl_3), 2-cloro-1,3-bis(metoxycarbonil)guanidina (Palau'Chlor), cloruro cianúrico y N-clorosuccinimida.

5. El proceso de acuerdo con la reivindicación 1, en donde el complejo de hierro (III) con la caseína N-acetil-L-aspartilada obtenida en la etapa (c) es clarificado antes de ser colocado en desecación o secado por atomizador o secado por congelación.
6. Un proceso para la preparación de una composición farmacéutica que comprende un complejo de hierro (III) con caseína N-acetil-L-aspartilada de grado alimenticio, en donde dicho proceso comprende el proceso de acuerdo con cualquiera de las reivindicaciones 1 a 5 y la combinación de dicho complejo de hierro (III) con caseína N-acetil-L-aspartilada de grado alimenticio con excipientes farmacéuticos, en particular seleccionados a partir de diluyentes y conservantes.

D3 JSR Jan 2016

COPIA DOCUMENTO D3

RESEARCH REVIEW

Clin Drug Invest 2005; 25 (11): 679-689
1173-2563/05/0011-0679/\$34.05/0

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Overview of Clinical Trials in the Treatment of Iron Deficiency with Iron-Acetyl-Aspartylated Casein

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Contents

Abstract	679
1. Pharmacodynamics	681
1.1 Dose-Response Studies	681
1.2 Pharmacokinetic Studies	681
2. Clinical Trials	682
2.1 Open Clinical Trials	682
2.2 Controlled Clinical Trials	685
2.2.1 N-Acetyl-Aspartylated Casein (Fe-ASP) versus Iron Protein Succinylate	685
2.2.2 Fe-ASP versus Iron Gluconate	685
2.3 Safety and Tolerability	686
3. Discussion	686
4. Conclusions	687

Abstract

Iron therapy is necessary in a wide variety of clinical situations, and new formulations with improved tolerability and efficacy would be a welcome alternative to ferrous sulfate. A trivalent iron protein complex has been developed using an *N*-acetyl-aspartylated derivative of casein (Fe-ASP) for oral iron therapy. This paper provides an overview of the pharmacokinetic and clinical data on Fe-ASP use. To date, 704 paediatric and adult patients affected by iron deficiency anaemia with a wide variety of clinical histories (dietary, iron absorption defects, pregnancy, chronic or acute gastrointestinal haemorrhage) have been treated with Fe-ASP in 16 clinical trials including nine open and seven controlled trials. In healthy volunteers, Fe-ASP proved to be an efficient vehicle for providing iron with high bioavailability and more rapid and persistent increases in serum iron levels than ferritin. In open clinical trials, highly significant improvements in clinical and haematological parameters were observed after treatment with Fe-ASP in all categories of patients with iron deficiency anaemia. In controlled clinical trials, the changes in clinical and haematological profiles observed with Fe-ASP were

virtually identical to those seen with iron protein succinylate (IPS), and Fe-ASP also compared well with parenteral iron gluconate. No safety considerations were raised.

Fe-ASP shows high efficacy in iron-deficient anaemia treatment, and it is an extremely well tolerated iron vehicle. Fe-ASP represents a valid alternative to IPS and shows promise as a substitute for parenteral iron therapy in selected clinical situations.

Iron therapy is necessary in a wide variety of clinical situations including pregnancy, chemotherapy, acute or chronic haemorrhage, haemodialysis, inflammatory bowel disease, inadequate diet, and gastrointestinal surgery. In particular, iron therapy is indicated for the treatment of girls who at menarche have an inadequate diet. Nail fragility and hair loss are symptoms of iron deficiency that may be due to absorption defects. The most common iron therapy involving oral supplementation with ferrous sulfate is generally effective, although it may cause gastric irritation and mucosal damage,^[1] and gastrointestinal haemorrhage in some cases. Oral iron therapy can also cause a number of other adverse effects such as pyrosis, nausea, diarrhoea and even constipation at varying frequencies. In certain clinical situations, for example in haemodialysis patients who cannot maintain adequate iron stores, oral iron therapy is expected to fail. Moreover, in patients with disorders of the gastrointestinal tract such as ulcerative colitis, symptoms may be aggravated by oral iron therapy. In addition, some patients cannot tolerate oral inorganic iron therapy supplements. The alternative parenteral iron therapy is considerably more expensive and poses higher risks compared with oral iron therapy, including the potential for serious allergic reactions.^[2]

Iron absorption occurs primarily in the duodenum and jejunum,^[3] although the mechanisms behind its absorption and transport from the gut remain poorly understood. It is well known that the ionic state of iron, i.e. ferrous (Fe^{2+}) or ferric (Fe^{3+}),

greatly influences its absorption. However, regardless of its original form, when taken orally iron is rapidly oxidised to the Fe^{3+} state, which at the low pH of the stomach tends to precipitate. The ferric iron that remains soluble is absorbed by cells in the intestinal mucosa of the duodenum and upper jejunum, is bound to transferrin, and then enters the systemic circulation. Thus, the efficacy of ferrous sulfate therapy is limited by the intrinsic characteristics of the salt. This can be partly overcome by co-administration with weak chelators such as ascorbate or, more commonly, folic acid, which help to keep the iron soluble until it passes from the stomach.

Different iron formulations with higher tolerability and efficacy would be a welcome alternative to ferrous sulfate. In fact, considerable research has been devoted to this problem. From a pharmacological point of view, the ideal oral iron formulation would have a high ionisation capacity and therefore a high uptake capacity, accompanied by gastric tolerability. However, up to now few alternatives substantially different from the classic therapy of ferrous sulfate have emerged. Recent studies on haeme-iron have been encouraging, but important questions remain regarding its efficacy and safety, especially in haemodialysis patients.^[4]

An interesting approach is to complex iron with protein hydrolysates or with polypeptides. One such product is the trivalent iron complex, iron protein succinylate (IPS) or ITF282.^[5] The therapeutic efficacy of IPS has been demonstrated in iron deficient

cy anaemia accompanied by limited gastrointestinal adverse effects compared with ferrous sulfate.^[6-8] This is likely due to the fact that this compound is insoluble at the low pH of the stomach, thus avoiding the release of large concentrations of iron ions in the small intestine.^[9] A recent study comparing ferric polysaccharide and IPS suggested that although both compounds are well tolerated in paediatric patients, IPS is likely to be more effective in increasing iron stores.^[10]

Another trivalent iron protein complex has been developed using an *N*-acetyl-aspartylated derivative of casein, namely Fe-ASP. The therapeutic rationale behind such a compound is the same as that of IPS: such a derivative should restrict iron ion interaction with the gastric mucosa, thus preventing formation of poorly absorbed high molecular-weight ferric hydroxides. After hydrolysis of the complex by pancreatic proteases in the more alkaline pH of the duodenum,^[11] trivalent iron in a bioavailable form is then absorbed in the small intestine. Fe-ASP would thus be expected to have pharmacological properties similar to those of IPS, providing an efficient vehicle for iron with an extremely favourable tolerability and safety profile.

This article provides an overview of the available pharmacokinetic and clinical data on the therapeutic use of Fe-ASP. To date, over 700 paediatric and adult patients affected by iron deficiency anaemia with a wide variety of pathologies and clinical situations have been treated in both open and controlled clinical trials with Fe-ASP.

1. Pharmacodynamics

Fe-ASP is a ferric iron complex obtained by salting out between the carboxyl groups present in the *N*-acetyl-aspartylate derivative of casein. This compound can function as a trivalent iron carrier, so that ferrous iron can acquire greater bioavailability and elevated gastric tolerability. The compound re-

mains insoluble at the acid pH of the stomach and becomes soluble at the higher pH in the duodenum.

1.1 Dose-Response Studies

Initial dose-response studies were carried out in 60 patients with iron deficiency anaemia using three different doses of Fe-ASP (2×20 mg/day, 2×40 mg/day, and 2×60 mg/day) for 2 months.^[12] The lowest dose caused statistically significant improvements in haemoglobin (Hb) and ferritin levels, while the intermediate dose produced normalisation of all haematological parameters. The highest dose did not cause any statistically significant differences in the therapeutic index compared with the intermediate one. As it showed the most favourable risk/benefit ratio, the dose of 2×40 mg/day was chosen for future clinical studies.

1.2 Pharmacokinetic Studies

Three different types of pharmacokinetic studies have been carried out in a small number of fasting healthy volunteers using a single oral dose of Fe-ASP 80mg. In the first study, 36 subjects were divided into three groups (12 subjects per group), and were treated with a single oral dose of Fe-ASP 80mg, ferritin corresponding to 80mg iron, or placebo.^[13] Serum iron levels were then determined at various time points (figure 1). At 30 minutes, significantly higher iron levels were observed in subjects treated with Fe-ASP compared with those obtained with either ferritin or placebo. Furthermore, these levels were maintained for 3 hours. Ferritin was characterised by a similar kinetic behaviour, although the increases in serum iron levels were not so rapid or long lasting.

In a single-blind, crossover study in healthy volunteers (12 subjects per group), repeated administration of Fe-ASP 80mg or placebo for 8 consecutive days was examined (figure 2).^[14] After one week of daily treatment, the kinetic changes in serum iron

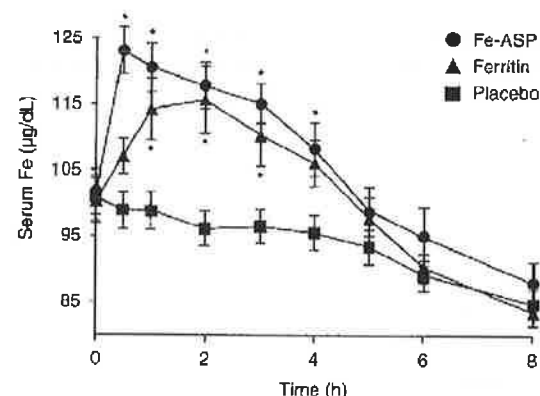


Fig. 1. Time-course of alterations in serum iron (Fe) concentration following administration of *N*-acetyl-aspartylated casein (Fe-ASP) 80mg, ferritin corresponding to 80mg of iron, or placebo to healthy volunteers. The results shown are the average of values in each group ($n = 12$). The asterisks indicate a statistically significant difference compared with the placebo group ($p < 0.01$).

levels were identical to those observed after a single dose of Fe-ASP.

In the third study, the bioavailability of Fe-ASP was assessed during the fasting phase and immediately before meals (12 subjects per group).^[15] The changes in serum iron levels after Fe-ASP administration were not significantly altered by fasting or administration prior to mealtime, and in both conditions significant increases were observed.

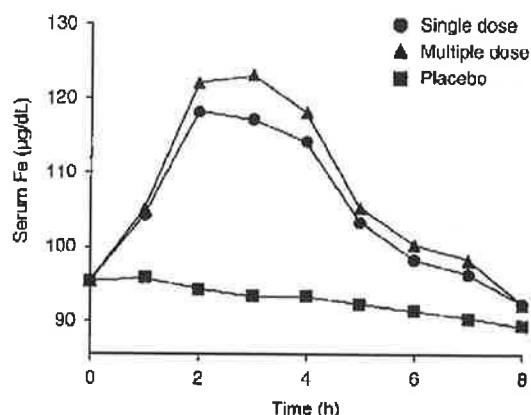


Fig. 2. Time-course of alterations in serum iron (Fe) concentration following administration of single or repeated doses of *N*-acetyl-aspartylated casein (Fe-ASP) 80mg or placebo to healthy volunteers. The results shown are the average of values in each group ($n = 12$).

2. Clinical Trials

The efficacy of Fe-ASP has been evaluated in several clinical trials in both adult and paediatric patients, by analysis of haematological parameters and clinical observation. Nine open and seven controlled trials have been carried out, involving 704 patients affected by iron deficiency and treated with Fe-ASP (table I and table II). In adult patients, Fe-ASP was given at 2×40 mg/day. The inclusion criteria varied widely and comprised patients with primary iron deficiency anaemia (dietary, iron absorption defects, pregnancy) and secondary iron deficiency (chronic or acute haemorrhage, e.g. peptic ulcer, gastrointestinal surgery or trauma); the majority of patients had iron deficiency related to pregnancy or haemorrhage. Fe-ASP was administered for periods ranging from 15 days to 5 months: 14.2% <60 days, 69.8% 61–90 days, and 16.0% >90 days.

2.1 Open Clinical Trials

In the open clinical trials of paediatric patients with iron deficiency, the duration of treatment with Fe-ASP varied from 30 to 60 days using doses of 2–4 mg/kg twice daily. In all situations, highly significant increases in serum iron levels were observed (table I). Objective improvement of clinical symptoms was accompanied by significant increases in both Hb and serum iron levels. Fe-ASP was well tolerated and no adverse effects were observed, even in premature newborns (24 subjects, gestational age 28–36 weeks).^[16,17]

In adult patients, the duration of Fe-ASP therapy (2×40 mg/day) was longer, ranging from 60 days to 5 months. As in paediatric patients, significant increases in Hb and serum iron levels and gradual improvements in clinical symptoms were observed. Furthermore, Fe-ASP was well tolerated by all patients.

Table 1. Open clinical studies with re-acylated, sequentially administered darbepoetin (Fe-ASP)

No. of patients (age range)	Inclusion criteria	Duration of therapy	Average Hb (g/dL)		Average serum iron concentration (µg/dL)		Reference
			initial	final	initial	final	
Paediatric^a							
50 (6 months–14 years)	Primary and secondary IDA	30–60 days	10.5	12.2	33	68	Zanin ^[16]
40 (24 premature, 16 full-term infants)	Primary IDA, premature birth	30–60 days	9.8	10.5	38	111	Ramenghi ^[17]
Adult^b							
40 (8–82 years)	IDA secondary to gastric haemorrhage	120 days	10.4	12.4	35	54	Veneroni ^[18]
35 (42–85 years)	Secondary IDA	45 days	10.5	11.4	36	46	Leone ^[19]
80 (38–82 years)	IDA secondary to gastric or uterine haemorrhage	60 days	10.6	12.0	34	62	Teti ^[20]
30 (42–85 years)	Secondary IDA	60 days	10.4	12.0	37	52	D'Amico ^[21]
66 (23–85 years)	IDA secondary to GI haemorrhage	5 months	8.4	12.7	27	64	Teti ^[22]
40 (64–88 years)	Secondary IDA	120 days	10.0	13.5	23	62	Roveri ^[23]
176 (15–40 years)	Secondary IDA in pregnancy and nursing patients	4 months	7.9	12.2	27	60	Szjarto ^[24]

a The dose of Fe-ASP was 2 × 2–4 mg/kg/day in paediatric patients and 2 × 40 mg/day in adult patients.

GI = gastrointestinal; Hb = haemoglobin; IDA = iron deficiency anaemia.

a The dose of Fe-ASP was 2 × 2–4 mg/kg/day in paediatric patients and 2 × 40 mg/day in adult patients.

GI = gastrointestinal; Hb = haemoglobin; IDA = iron deficiency anaemia.

Table II. Controlled clinical studies with N-acetyl-L-aspartylated casein (Fe-ASP)

Study design	Patients (n)	Inclusion criteria	Duration (days)	Average Hb (g/dL)		Average serum iron concentration (µg/dL)		Reference
				initial	final	initial	final	
Paediatric ^a								
Double-blind	Fe-ASP 20 Pemexin ^b 20	Primary and secondary IDA	40–90	11.0 10.0	12.0 11.0	27 25	53 60	Burgio ^[24]
Adult ^c								
Single-blind	Fe-ASP 31	IDA secondary to GI haemorrhage	15	8.4 7.8	9.9 10.2	27 23	41 46	Teti ^[25]
Controlled	Fe-ASP 20 Ferilix [®] 20	IDA secondary to GI surgery	15	10.0 10.0	13.5 12.8	23 20	62 58	Zappalà ^[26]
Controlled	Fe-ASP 22 Pemexin 20	IDA secondary to haemorrhage, pregnancy	30–60	10.9 11.0	12.3 12.7	19 26	59 69	Candiani ^[27]
Single-blind	Fe-ASP 19 Pemexin 19	Secondary IDA	30	10.7 10.9	11.0 11.9	39 39	50 44	Dordin ^[28]
Controlled	Fe-ASP 15 Pemexin 15	Secondary IDA	30	10.5 10.5	12.1 11.5	38 38	47 39	Colombo ^[29]
Randomised, double-blind	Fe-ASP 20 Pemexin 20	Secondary IDA	60	10.9 11.0	11.7 11.8	37 38	53 55	Renzi ^[30]
Single-blind	Fe-ASP 31	IDA secondary to GI haemorrhage	15	8.4 7.8	9.9 10.2	27 23	41 46	Teti ^[25]

a In paediatric patients, the dose of both Fe-ASP and Pemexin was 4 mg/kg/day.

b Iron protein succinylate.

c Iron gluconate.

GI = gastrointestinal; Hb = haemoglobin; IDA = iron deficiency anaemia.

Table III. Average percentage changes in principal haematological parameters in open clinical trials with *N*-acetyl-aspartylated casein

Parameter	Patient group	
	paediatric	adult
Haemoglobin	+6	+23
Reticulocytes	+53	+61
Mean corpuscular volume	+4	+4
Serum iron	+46	+40
Serum ferritin	+110	+38
Transferrin	+0.8	+0.9

Table III shows the average variations in the main haematological parameters detected in the open trials with Fe-ASP. Improvements in these parameters were similar in all categories of patients studied (general medicine, gynaecological, etc.). In the largest study involving 176 patients, normalisation of all haematological parameters was observed in gynaecological patients (pregnant and nursing mothers) after 4 months' treatment with Fe-ASP. Fe-ASP was especially well tolerated in these patients and no adverse reactions were recorded.^[1,2,16-23]

In all the open trials (table IV), the clinical efficacy and tolerability were scored as good, satisfactory or unsatisfactory on an ordinal scale. The efficacy of Fe-ASP was considered good or satisfactory in 79% of cases, and tolerability was classified as good in 96.6% of cases. There were no safety concerns in any case.

2.2 Controlled Clinical Trials

Fe-ASP has been compared with existing treatments in seven clinical trials (table II), including one paediatric and six adult studies. Five of these studies compared Fe-ASP with IPS (Pernexin 40®, Schering SpA, Milan, Italy)¹, while in the other two studies iron gluconate (Ferlixit®, Aventis SpA, Milan, Italy) was used as a reference.

2.2.1 *N*-Acetyl-Aspartylated Casein (Fe-ASP) versus Iron Protein Succinylate

In the clinical trial of paediatric patients with iron deficiency, the period of treatment ranged from 40 to 90 days.^[24] Both Fe-ASP and IPS were administered at doses of 2–4 mg/kg twice daily. Highly significant improvements in clinical and haematological parameters were observed in all paediatric patients with both compounds (table II). In fact, the clinical and haematological profiles were nearly identical for IPS and Fe-ASP, and significant increases were observed in both Hb and serum iron levels. It should be noted that Fe-ASP was well tolerated and no adverse effects were observed, while two of the paediatric patients treated with IPS had severe gastrointestinal reactions (nausea and diarrhoea) that necessitated discontinuation of treatment.

In the four trials conducted on adult patients, treatment was given for 30–60 days with identical doses (2 × 40 mg/day) for both drugs.^[27-30] As was seen in the paediatric study, the clinical and haematological profiles were nearly identical in the Fe-ASP and IPS treatment groups, with significant increases in Hb and serum iron levels. Both drugs showed nearly identical efficacy. Mild adverse events, consisting of gastric intolerance (pyrosis, nausea and vomiting) and diarrhoea were observed in six patients, two of whom belonged to the Fe-ASP group (2.6%) and four to the IPS group (5.4%).

2.2.2 Fe-ASP versus Iron Gluconate

Two clinical trials compared the efficacy and safety of Fe-ASP with those of iron gluconate in adult patients affected by iron deficiency anaemia due to gastrointestinal surgery or chronic gastrointestinal haemorrhage.^[25,26] In both studies, the two treatments were associated with significant improvements in clinical and haematological parameters, including significant increases in Hb and serum

¹ The use of trade names is for product identification purposes only and does not imply endorsement.

Table IV. Global clinical judgment in controlled clinical trials with *N*-acetyl-aspartylated casein (Fe-ASP)^[24-30]

Clinical judgement	Fe-ASP		IPS and iron gluconate	
	efficacy (%)	tolerability (%)	efficacy (%)	tolerability (%)
Good	64.3	96.6	54.4	89.2
Satisfactory	33.6	2.0	30.2	8.3
Unsatisfactory	2.1	1.4	15.4	2.5

IPS = iron protein succinylate.

iron levels. One case of diarrhoea per treatment group was reported. No other adverse events were observed.

The average percentage variations of the main haematological parameters seen with Fe-ASP in all the controlled trials are detailed in table IV.^[24-30] The global scores for clinical efficacy and tolerability are shown in table V. Fe-ASP was considered to be good or satisfactory in 97.9% of cases, compared with 84.6% of reference drug cases.

2.3 Safety and Tolerability

In the open trials involving 557 patients, only one adverse reaction was recorded. This concerned a case of mild abdominal pain occurring in a patient with gastric haemorrhage that spontaneously resolved within 48 hours.

In the controlled trials involving 147 subjects, three patients (2%) treated with Fe-ASP reported an adverse event. It should be noted that, across all clinical trials, a total of only four adverse events in 704 cases (0.6%) were observed. All these events (gastrointestinal disturbances and diarrhoea) may be

classified as mild and did not require therapy suspension. No safety concerns were raised with Fe-ASP. The tolerability was classified as good or satisfactory in 98.6% of patients.

3. Discussion

The main characteristic of the new iron protein complex Fe-ASP is that it restricts iron ion interaction with the gastric mucosa, preventing formation of poorly absorbed high molecular-weight ferric hydroxides. Iron, in a bioavailable form, is then absorbed in the small intestine after hydrolysis of the complex by pancreatic proteases in the more alkaline pH of the duodenum.^[11] In this way, most of the adverse effects associated with ferrous sulfate administration are avoided, since ferrous sulfate shows a reduced absorptive capacity and a higher frequency of adverse events after long-term therapy.

Dose-response studies demonstrated that 80mg of Fe-ASP is able to elicit an extremely rapid increase in serum iron levels. Compared with ferritin, the increases in serum iron following administration of Fe-ASP were observed earlier and lasted longer. Thus, Fe-ASP provides a rapid and sustained source of bioavailable iron at doses identical to those used for IPS, another iron protein complex.

Furthermore, multiple doses of Fe-ASP lead to increases in serum iron that are indistinguishable from those observed after a single dose. This characteristic makes Fe-ASP ideal for long-term or repeated therapy. In fact, excellent tolerability was observed even with therapeutic regimens lasting up to 5 months. Moreover, the bioavailability of Fe-ASP was unchanged when taken during the fasting phase

Table V. Average percentage changes in principal haematological parameters in controlled clinical trials with *N*-acetyl-aspartylated casein (Fe-ASP)^[24-30]

Parameter	Fe-ASP	IPS and iron gluconate
Haemoglobin	+15	+20
Reticulocytes	+105	+98
Mean corpuscular volume	+7	+7
Serum iron	+31	+40
Ferritin	+62	+59
Saturated transferrin	+160	+136

PS = iron protein succinylate.

at mealtime. Conversely, ferrous sulfate is better taken with food or following meals in order to minimise gastric irritation.

The results of the clinical trials in 704 patients with iron-deficiency anaemia demonstrated that Fe-ASP possesses a high degree of efficacy and is very well tolerated. A total of 174 gynaecological patients were included in the open trials, including pregnant and nursing women, and no adverse effects were observed. The high degree of gastric tolerability makes Fe-ASP ideally suited for the long-term treatment of such patients. Similarly, IPS has been shown to be better tolerated in pregnant women than ferrous sulfate or iron-polystyrene sulfonate.^[7]

The results of controlled clinical trials with Fe-ASP demonstrated that it is similar in efficacy to IPS. This finding was expected since both products have a similar chemical profile.^[5] IPS has been widely studied and it has been shown to be effective in both paediatric and adult patients.^[6,7,31,32] The frequency of adverse effects of IPS has been reported to range from 2.4% to 11.5%.^[6,7,31,32] In a multicentre study involving over 1000 patients, IPS had a favourable clinical profile in 78.9% of patients,^[6] which is in general agreement with other studies.^[7,31,32] Although different scales were used, it is interesting to note that Fe-ASP was classified as good or satisfactory in 98.6% of patients and it was considered well tolerated in 98.6% of the 704 cases analysed. Despite the temptation to speculate that Fe-ASP has a more favourable tolerability and efficacy profile compared with IPS, larger head-to-head studies are required to prove such a hypothesis. To date, the controlled clinical trials comparing Fe-ASP and IPS have only included a total of 96 patients.^[24-30] Four adverse reactions were observed in the IPS-treated group (5.4%) compared with two in the Fe-ASP group (2.6%). However, the number of cases evaluated is too small to draw any definitive conclusions. In this limited number of patients, both

Fe-ASP and IPS showed nearly identical efficacy profiles.

Two studies have compared the efficacy and therapeutic safety of Fe-ASP with those of parenteral iron.^[25,26] Even in these small patient groups, Fe-ASP performed well, showing efficacy and tolerability profiles similar to those of iron gluconate. This is not a trivial point, as parenteral therapy carries greater risks and higher costs compared with oral treatment. As such, parenteral iron therapy is generally reserved for patients with disorders of the gastrointestinal tract, i.e. ulcerative colitis, in which symptoms may be aggravated by oral iron therapy. It is also commonly used in patients with high rates of haemorrhage, in patients undergoing haemodialysis who are unable to maintain iron balance, and in pregnancy.^[33-36] Further investigation of Fe-ASP in these categories of patients would be of particular interest as it could provide a therapy with fewer risks than parenteral iron, while retaining similar therapeutic benefits. A preliminary study suggests that such a strategy is possible; during a 6-month study oral haeme iron polypeptide effectively replaced parenteral iron therapy in the majority of haemodialysis patients.^[4]

The search for other oral iron supplements has also included caseinophosphopeptides that, at least in experimental models, have been suggested to cure anaemia and showed a more favourable tissue uptake compared with ferrous sulfate.^[37] Based on the available clinical studies, Fe-ASP appears to represent a compelling alternative to ferrous sulfate and IPS. The studies presented in this review indicate that Fe-ASP is effective and well tolerated in patients requiring oral iron therapy. However, one limitation that should be noted is that these trials have not been published.

4. Conclusions

Although ferrous sulfate preparations exhibit a relatively low frequency of adverse events, which

are of limited clinical concern, it is still desirable to decrease both the incidence and duration of these events without compromising clinical efficacy. The requirements for a more biologically suitable compound are effectively met with Fe-ASP, in which iron is reversibly bound to a protein carrier. Oral administration of Fe-ASP results in a rapid rise in bioavailable iron, which is also sustained.

As a treatment for iron-deficient anaemia, Fe-ASP shows high efficacy as judged by both clinical and haematological observations. In addition, Fe-ASP is extremely well tolerated and is a safe iron vehicle for the wide spectrum of paediatric and adult patients needing oral iron therapy. Fe-ASP represents a valid alternative to IPS and may even show promise as a substitute for parenteral iron therapy in selected clinical situations.

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