

Señor Director
DIRECCIÓN DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 11-180686-00014-0000

Fecha: 2014-01-10 14:59:08
Tra. 11 PATENTEIYII
Act. 523 RESPUESTA

Dep. 2020 DIR.NUEVASCR
Eve: 378 FASENACIONALI
Folios: 54

Trámite : 011
Evento : 378
Actuación : 523

Referencia : Expediente No. **11.180.686**
Asunto : Solicitud de patente para: **"COMPOSICIONES FARMACÉUTICAS SÓLIDAS QUE COMPRENDEN IRBESARTÁN Y BESILATO DE AMLODIPINA Y EXCIPIENTES FARMACÉUTICAMENTE ACEPTABLES, EN DONDE EL IRBESARTÁN ESTÁ SEPARADO FÍSICAMENTE DEL BESILATO DE AMLODIPINA"**
Solicitante : **SANOFI**
Fecha de solicitud : 29 de Diciembre de 2011

1. Yo, Luz Clemencia DE PÁEZ, en mi condición de apoderada de la sociedad solicitante de la patente de la referencia, me refiero al oficio No. **19057** notificado por fijación en lista el 15 de Octubre de 2013.

2. Mediante oficio No. **19057** se puso en conocimiento del solicitante el informe que contiene las observaciones hechas por su Despacho sobre la presente solicitud de patente. Las observaciones realizadas en el oficio se refieren a la claridad del pliego reivindicatorio, a la claridad del título, a la novedad de las reivindicaciones 1 a 5, 7 a 11 y 13 en vista del documento D1: WO2008044862, y al nivel inventivo de las reivindicaciones 1 a 13 en vista de los documentos D1: WO2008044862 y D2: US5994348.

3. Respuesta a las objeciones

De este modo y con el objeto de atender las objeciones arriba mencionadas, se desea presentar las siguientes modificaciones, aclaraciones y argumentos:

"EXCELENCIA LEGAL EN UN MUNDO SIN FRONTERAS"

BOGOTÁ - Edificio Siski - Carrera 4 No. 72 - 35 - Tel. (57-1) 347 3611 - Fax (57-1) 211 8650 - Fax In U.S.A: (1-305) 675 7743 - COLOMBIA
MEDELLÍN - San Fernando Plaza - Carrera 43 A No. 1 - 50 - Torre Protección Oficina 652 - Tel: (57-4) 604 4794 Ext. 6729 / 6731 - Fax: (57-4) 604 4731- COLOMBIA

www.cavelier.com
cavelier@cavelier.com

3.1 Modificación de una solicitud en trámite

De acuerdo con el artículo 34 de la Decisión 486 de la Comisión de la Comunidad Andina, donde se establece que la modificación de una solicitud es posible en cualquier momento del trámite mientras no implique una ampliación de la solicitud inicial, me permito presentar un nuevo pliego reivindicatorio conformado por 16 reivindicaciones.

El título se ha modificado de la siguiente manera:

“COMPOSICIONES FARMACÉUTICAS SÓLIDAS QUE COMPRENDEN IRBESARTÁN Y BESILATO DE AMLODIPINA Y EXCIPIENTES FARMACÉUTICAMENTE ACEPTABLES, EN DONDE EL IRBESARTÁN ESTÁ SEPARADO FÍSICAMENTE DEL BESILATO DE AMLODIPINA”

Se han introducido las siguientes modificaciones al capítulo reivindicatorio:

- La reivindicación 5 ha sido eliminada.
- La expresión '*preferiblemente*' ha sido eliminada de las reivindicaciones 7 a 9 y 13 (nuevas 6, 8, 10 y 16), y en consecuencia, se han introducido 4 reivindicaciones con las modalidades preferidas y dependientes de cada una de dichas reivindicaciones 7 a 9 y 13 (nuevas 6, 8, 10 y 16).
- La reivindicación 10 (nueva 12) ha sido modificada eliminando el fragmento '*después de 6 meses a 40%C/75% de HR*'.

Así, las reivindicaciones son ahora muy claras y precisas en el momento de señalar la naturaleza de la invención reivindicada y es evidente que las características técnicas esenciales de la invención están establecidas.

Por lo anterior, las objeciones formuladas por el Examinador en cuanto a la claridad y concisión del pliego reivindicatorio se ven superadas. En consecuencia, se solicita atentamente tener en cuenta este nuevo pliego reivindicatorio para el nuevo análisis de patentabilidad.

Con respecto a las objeciones realizadas por el señor Examinador hacia las reivindicaciones 1 y 12 (nueva 14), respetuosamente manifestamos nuestro desacuerdo por las siguientes razones:

3

- Con respecto a la reivindicación 1, amablemente ponemos de presente que los términos 'dosis fija' y 'estable' son expresiones que se encuentran dentro del preámbulo de la dicha reivindicación. Además, dichas expresiones son bien conocidas por una persona del oficio normalmente versada en la materia, pues son ampliamente utilizadas en el campo de la presente invención.
- Por otra parte, en referencia a la reivindicación 12 (nueva 14), atentamente indicamos que las reivindicaciones precedentes mencionan que la composición está exenta de lactosa, mientras que la reivindicación 12 (nueva 14) se refiere al proceso, en donde dicho proceso está exento de añadir lactosa. Por lo tanto, es claro que las reivindicaciones precedentes se refieren a un producto (composición) y la reivindicación 12 (nueva 14) se refiere al proceso de preparación de la composición, y en consecuencia, la reivindicación 12 (nueva 14) no debería ser eliminada.

En este sentido, teniendo en cuenta las anteriores aclaraciones y las modificaciones realizadas al pliego reivindicatorio, atentamente señalamos que las objeciones anteriormente argumentadas, con respecto a la claridad y concisión del pliego reivindicatorio carecen de validez y por lo tanto, se consideran superadas.

3.2 Argumentos a favor de la falta de Novedad

El artículo 16 de la Decisión 486 señala lo siguiente:

"Artículo 16: Una invención se considerará nueva cuando no esté comprendida en el estado de la técnica.

El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente, o en su caso, de la prioridad reconocida."

La novedad de una invención se evalúa a través de la comparación uno a uno de sus características esenciales. De este modo, una invención puede ser objetada por novedad cuando sus características esenciales son exactamente iguales a las de un antecedente que represente el estado de la técnica conocido al momento de presentar la

solicitud. Por lo tanto **en caso que llegue a existir al menos una diferencia en dicha comparación**, se afirma que la invención **SI** cumple con el requisito de novedad. 4

Con base en lo anterior, respetuosamente manifestamos nuestro desacuerdo con el análisis llevado a cabo por el Examinador y con las conclusiones del mismo y solicitamos atentamente la reconsideración de las razones por las cuales se objeta la novedad, con base en la siguiente información:

A este respecto, amablemente ponemos de presente que existe una diferencia técnica con respecto al documento D1, la cual consiste en que el comprimido monocapa de acuerdo a la presente invención está hecho de ambos compuestos activos, tanto de irbesartán como de amlodipina. A diferencia de la presente invención, en el documento D1, el núcleo **interno** es una monocapa que contiene exclusivamente amlodipina y la forma sólida final es un comprimido multi-capa de amlodipina e irbesartán. En otras palabras, la presente invención es diferente de la composición farmacéutica divulgada en D1.

De tal manera que, la invención reclamada en el nuevo pliego reivindicatorio es novedosa frente a las enseñanzas de D1 porque dicho documento no enseña un comprimido monocapa que comprende **irbesartán y amlodipina y únicamente invenciones** con todas las características técnicas identificadas en el mismo documento de la anterioridad **pueden afectar la novedad de invenciones reivindicadas en una solicitud presentada posteriormente y por lo tanto**, la objeción formulada a este respecto se debe tener por superada.

En consecuencia, de acuerdo con los argumentos anteriormente explicados, la invención de la presente solicitud de patente es novedosa sobre el documento del estado de la técnica D1 citado por el Examinador.

3.3 Argumentos a favor de la falta de Nivel Inventivo

El artículo 18 de la Decisión 486 señala lo siguiente:

“Artículo 18.- Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa

invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.”

Una invención se considerará inventiva si la misma no hubiese resultado obvia a partir del arte previo para una persona del oficio normalmente versada en la materia. Esto a su vez implica que el Examinador a cargo de esta evaluación debe colocarse en el momento exacto en el que el inventor buscaba resolver el problema técnico contemplado en la solicitud y para el cual poseía la literatura y el conocimiento disponibles en dicho momento.

Siguiendo entonces los lineamientos de la Jurisprudencia aplicable al análisis del nivel inventivo de una solicitud de patente, se considera que una anterioridad o una combinación de dos anterioridades puede afectar dicho requerimiento de patentabilidad, si una persona medianamente versada en la materia encuentra enseñanzas o sugerencias claras que, a partir de un conocimiento medio en dicho campo, le permitan llegar de manera obvia a la invención reivindicada. Adicionalmente se considera que una mejora sustancial, un efecto inesperado o una ventaja con respecto al arte previo es un indicio de nivel inventivo, por cuanto aporta un salto tecnológico en la regla técnica.

A este respecto, respetuosamente manifestamos nuestro desacuerdo con el análisis llevado a cabo por el Examinador y con las conclusiones del mismo y solicitamos atentamente la reconsideración de las razones por las cuales se objeta el nivel inventivo, con base en la siguiente información:

Con respecto al nivel inventivo, la esencia de la presente invención reside en la provisión de comprimidos monocapa farmacéuticas que comprenden irbesartán y besilato de amlodipina, en donde el besilato de amlodipina no sufre degradación y el comprimido ha reducido el nivel de impurezas totales en la estabilidad a largo plazo. Adicionalmente, entre los beneficios inesperados, la configuración reivindicada del comprimido monocapa inventivo proporciona un perfil de disolución equivalente al correspondiente a la combinación libre de liberación inmediata de los mismos compuestos activos.

La característica que distingue la invención reivindicada de la enseñanza del documento D1 reside en la presencia de un comprimido de irbesartán y besilato de amlodipina, en donde únicamente el irbesartán está en el material intragranular, los gránulos de irbesartán siendo embebidos en una matriz extragranular que comprende

besilato de amlodipina, en donde el comprimido es un comprimido monocapa y ambos tanto el irbesartán como la amlodipina son liberados inmediatamente.

Esta característica hace la composición reivindicada ventajosa ya que muestra impurezas reducidas y controladas cuando se somete a estudios de estabilidad de la tensión (Ejemplo 5 de la presente descripción).

Esta solución de acuerdo a la invención no es obvia en vista del documento D1, ya que D1 no hace comentarios sobre este problema de estabilidad y nivel reducido de impurezas. A primera vista, la referencia D1 no proporciona a una persona del oficio normalmente versada en la materia con ninguna guía de cómo lograr esto, menos aún proporciona ninguna motivación para modificar el comprimido bi-capa de irbesartán de liberación inmediata y amlodipina de liberación inmediata retardada de D1 tal como para llegar al objeto de las presentes reivindicaciones. Además, D1 tiene una configuración de comprimido multicapa especialmente designada para lograr liberación inmediata de un activo (por ejemplo, irbesartán) pero una liberación gradual de los otros (por ejemplo, amlodipina). De tal manera que, una persona versada en la materia no se vería motivada a modificar el el comprimido de amlodipina retardada multicapa de D1, tal como lo propone el Señor Examinador, de modo que tenga un perfil de disolución de amlodipina adecuado exento de amlodipina tal como los resultados del comprimido monocapa reivindicado en la presente solicitud.

Por lo tanto, un técnico con conocimientos medios en la materia no estaba en condiciones de plantearse el problema, tampoco de resolverlo en la forma en que se reivindica y tampoco de prever el resultado, por lo que la presente solicitud posee la altura inventiva para que se le conceda el privilegio solicitado.

En consecuencia de lo anterior, la invención de la presente invención tiene nivel inventivo en vista de los documentos D1 y D2 del estado de la técnica citados por el Examinador.

3.4 Concesión de Solicitudes equivalentes

Si bien entendemos y aceptamos que cada país es autónomo en la concesión o negación de los privilegios de patente, queremos resaltar el hecho que el análisis de los requisitos para el otorgamiento de esos derechos es prácticamente universal. La presente

invención fue concedida por la Oficina de Patentes de Europa, patente No. EP2448561 (B1); Marruecos, patente No. MA33463 (B1); España, patente No. ES2435240 (T3) y República de Croacia, patente No. HRP20131088 (T1).

3.5 Conclusión

Por todo lo anterior, el documento D1 no resulta una anterioridad válida capaz de afectar la novedad de la invención de la presente solicitud. De la misma manera, el documento D1, el documento D2, o su combinación, no resultan anterioridades válidas capaces de afectar el nivel inventivo de la invención de la presente solicitud. Por lo tanto, consideramos que el Examinador está pasando por alto que una sola diferencia con respecto al estado de la técnica, permite concluir que el objeto reivindicado es nuevo. Además, está excluyendo el hecho de que el inventor en el momento de solucionar el problema técnico de la solicitud tuvo que emplear habilidad inventiva, pues la presente invención no resulta de la mera extrapolación de las enseñanzas del arte previo, como se afirma. Se está desconociendo el mérito investigativo empleado y que está aportando una ventaja al arte previo.

4. Puesto que se ha dado respuesta a todas las objeciones formuladas por el Examinador, se solicita atentamente proceder al otorgamiento de la solicitud de patente. En este sentido, respetuosamente recordamos al Examinador que la patente no podrá ser negada con base en objeciones diferentes a las expuestas en la acción oficial No. 19057, toda vez que al no haber sido trasladadas a mi representada, dicha decisión violaría tanto el tenor literal del artículo 45 de la Decisión 486 como el derecho constitucional al debido proceso. En este evento, y con base en el inciso 2 del artículo 45, respetuosamente solicitamos al Examinador expedir una nueva acción oficial que permita a mi representada contra argumentar las mismas o modificar la solicitud con el fin de cumplir los requisitos de patentabilidad.

De otro lado, respetuosamente manifiesto que a pesar de eliminar materia del pliego reivindicatorio originalmente presentado, mi representada no renuncia a la protección que pueda obtener sobre dicha materia y se reserva el derecho de presentar una solicitud divisional que la contenga durante el trámite de la presente solicitud, beneficiándose de la fecha de prioridad inicialmente reivindicada.

5. Anexos

- Nuevo pliego reivindicatorio conformado por 16 reivindicaciones
- Copia de la patente equivalente concedida en Europa

Señor Director,


LUZ CLEMENCIA DE PAÉZ

C.C. 35.456.344 de Usaquén

T.P.A. No. 23.555

nm
COLO-00751-0264-009-0
COLO-00751-0264-010-8
COLO-00751-0264-008-2
COLO-00751-0841-035-7
SGD\SGD\ID-258200\WPCL0751
No. M-2014-258200\SGD

REIVINDICACIONES

- 1) Una composición de dosis fija farmacéutica, oral, sólida, estable, en forma de un comprimido monocapa que comprende irbesartán, besilato de amlodipina y excipientes farmacéuticamente aceptables, en la que el irbesartán está separado físicamente del besilato de amlodipina y en donde el irbesartán, bajo la forma de gránulos recubiertos, está incorporado en una matriz extragranular que comprende besilato de amlodipina.
- 2) La composición según la reivindicación 1, en donde el comprimido está recubierto de película.
- 3) La composición según una cualquiera de las reivindicaciones 1 a 2, en la que el irbesartán representa entre 20% y 70% en peso de la composición total.
- 4) La composición según una cualquiera de las reivindicaciones 1 a 3, en la que el besilato de amlodipina representa entre 1% y 20% en peso de la composición total.
- 5) La composición según una cualquiera de las reivindicaciones 1 a 4, en la que dicha composición sólida está exenta de lactosa.
- 6) La composición sólida según una cualquiera de las reivindicaciones 1 a 5, en la que la cantidad de Irbesartán está comprendida entre 150 mg y 300 mg del peso total del comprimido.
- 7) La composición sólida según la reivindicación 6, en la que la cantidad de Irbesartán es 300 mg o 150 mg del peso total del comprimido.
- 8) La composición sólida según una cualquiera de las reivindicaciones 1 a 7, en la que la cantidad de besilato de amlodipina está comprendido entre 5 mg y 10 mg del peso total del comprimido.
- 9) La composición sólida según la reivindicación 8, en la que la cantidad de

besilato de amlodipina es 7 mg o 14 mg del peso total del comprimido.

10) La composición sólida según una cualquiera de las reivindicaciones 1 a 9, en la forma de un comprimido, en la que el peso total del comprimido está entre 400 mg y 600 mg.

11) La composición sólida según la reivindicación 10, en la forma de un comprimido, en la que el peso total del comprimido es 500 mg.

12) La composición según una cualquiera de las reivindicaciones 1 a 11, que tiene menos del 1,50% (p/p) de impurezas totales para Amlodipina y menos de 0,50% (p/p) de impurezas totales para Irbesartán.

13) Un procedimiento para la preparación de una composición farmacéutica oral estable en forma de un comprimido monocapa que comprende irbesartán y besilato de amlodipina, en que el procedimiento comprende las etapas de:

- i. granular irbesartán y uno o más excipientes farmacéuticamente aceptables, con disolución acuosa que contiene un aglutinante, para formar gránulos;
- ii. secar los gránulos;
- iii. mezclar por separado besilato de amlodipina con excipientes farmacéuticamente aceptables;
- iv. mezclar los gránulos de irbesartán de la etapa ii) con la mezcla de besilato de amlodipina de la etapa iii);
- v. lubricar la mezcla de la etapa iv); opcionalmente después de una etapa de pre-lubricación; y
- vi. comprimir la mezcla en comprimidos.

14) El procedimiento según la reivindicación 11, en el que el grupo de excipientes farmacéuticamente aceptables usados en la etapa i) y iii) del proceso está exento de lactosa.

15) El procedimiento según una cualquiera de las reivindicaciones 11 a 12, en el que la etapa de prelubricación comprende mezclar la mezcla de la etapa (iv) durante 10 a 25 min, antes de realizar la etapa de lubricación.

16) El procedimiento según la reivindicación 15, en el que la etapa de prelubricación comprende mezclar la mezcla de la etapa (iv) durante 20 min antes de realizar la etapa de lubricación.

SGD\SGD\ID-258196\WPCL0751



European Patent Office
Postbus 5818
2280 HV RIJSWIJK
NETHERLANDS
Tel. +31 (0)70 340-2040
Fax +31 (0)70 340-3016

12



Taravella, Brigitte
Sanofi
Département Brevets
54, rue La Boétie
75008 Paris
FRANCE

For any questions about
this communication:
Tel.: +31 (0)70 340 45 00

Date
16.08.13

Reference FR2009/028	Application No./Patent No. 09744185.1 - 1455 / 2448561
Applicant/Proprietor SANOFI	

Transmission of the certificate for a European patent pursuant to Rule 74 EPC

The certificate for a European patent is herewith transmitted.

The European patent specification can be downloaded from the EPO publication server
<https://data.epo.org/publication-server/> (see OJ EPO 2005, 126).

Note:

A corrected title page of the European patent specification will be published, if the bibliographic data have been changed after completion of the technical preparations.

For the Examining Division





European Patent Office
Postbus 5818
2280 HV RIJSWIJK
NETHERLANDS
Tel. +31 (0)70 340-2040
Fax +31 (0)70 340-3016



Taravella, Brigitte
Sanofi
Département Brevets
54, rue La Boétie
75008 Paris
FRANCE

For any questions about
this communication:
Tel.: +31 (0)70 340 45 00

Date
18.07.13

Reference FR2009/028	Application No./Patent No. 09744185.1 - 1455 / 2448561
Applicant/Proprietor SANOFI	

Decision to grant a European patent pursuant to Article 97(1) EPC

Following examination of European patent application No. 09744185.1 a European patent with the title and the supporting documents indicated in the communication pursuant to Rule 71(3) EPC dated 08.03.13 is hereby granted in respect of the designated Contracting States.

Patent No. : 2448561
Date of filing : 17.09.09
Priority claimed : 30.06.09/INA DE13412009

Designated Contracting States
and Proprietor(s) : AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT
LU LV MC MK MT NL NO PL PT RO SE SI SK SM TR
SANOFI
54, rue La Boétie
75008 Paris/FR

This decision will take effect on the date on which the European Patent Bulletin mentions the grant (Art. 97(3) EPC).

The mention of the grant will be published in European Patent Bulletin 13/33 of 14.08.13.

Examining Division

de Sousa Palma V

Konter J

Dudás E



Registered letter
EPO Form 2006A 12.07 (11/07/13)

to EPO postal service: 12.07.13

ANMERKUNG ZUR ENTSCHEIDUNG ÜBER DIE ERTEILUNG
EINES EUROPÄISCHEN PATENTS (EPA Form 2006)

1. **EPA Informationsbroschüre "Nationales Recht zum EPÜ"**
Diese Broschüre enthält nützliche Informationen zu den formalen Erfordernissen und den Handlungen, die vor den Patentbehörden der Vertragsstaaten vorzunehmen sind, um Rechte in diesen Staaten zu erlangen. Da diese Handlungen einem ständigen Wandel unterworfen sind, sollte immer nur die neueste Ausgabe der Broschüre benutzt werden. Nachträgliche Informationen werden im Amtsblatt veröffentlicht.
2. **Übersetzung der europäischen Patentschrift nach Artikel 65 (1) des Europäischen Patentübereinkommens**
Sie werden erneut darauf hingewiesen, dass bestimmte Vertragsstaaten nach Artikel 65 (1) EPÜ eine Übersetzung der europäischen Patentschrift verlangen; hierauf wird in der Mitteilung gemäß Regel 71 (5) EPÜ verwiesen. Die Nichteinreichung dieser Übersetzung kann zur Folge haben, dass das Patent in dem betreffenden Staat/in den betreffenden Staaten als von Anfang an nicht eingetreten gilt. Weitere Einzelheiten entnehmen Sie bitte der oben genannten Broschüre.
3. **Zahlung von Jahresgebühren für europäische Patente**
Nach Artikel 141 EPU können "nationale" Jahresgebühren für das europäische Patent für die Jahre erhoben werden, die an das Jahr anschließen, in dem der Hinweis auf die Erteilung des europäischen Patents im "Europäischen Patentblatt" bekanntgemacht wird. Weitere Einzelheiten entnehmen Sie bitte der oben genannten Broschüre.

NOTE RELATING TO THE DECISION TO GRANT A
EUROPEAN PATENT (EPO Form 2006)

1. **EPO Information Brochure "National law relating to the EPC"**
This brochure provides useful information regarding formal requirements and the steps to be taken before the patent authorities of the Contracting States in order to acquire rights in those states. Since the necessary steps are subject to change the latest edition of the brochure should always be used. Subsequent information is published in the Official Journal.
2. **Translation of the European patent application under Article 65(1) of the European Patent Convention**
Your attention is again drawn to the requirements regarding translation of the European patent specification laid down by a number of Contracting States under Article 65(1) EPC, to which reference is made in the communication under Rule 71(5) EPC. Failure to supply such translation(s) may result in the patent being deemed to be void "ab initio" in the State(s) in question. For further details you are recommended to consult the above-mentioned brochure.
3. **Payment of renewal fees for European patents**
Under Article 141 EPC "national" renewal fees in respect of a European patent may be imposed for the years which follow that in which the mention of the grant of the European patent is published in the "European Patent Bulletin". For further details you are recommended to consult the above-mentioned brochure.

REMARQUE RELATIVE A LA DECISION DE DELIVRANCE
D'UN BREVET EUROPEEN (OEB Form 2006)

1. **Brochure d'information de l'OEB "Droit national relatif à la CBE"**
Cette brochure fournit d'utiles renseignements sur les conditions de forme requises et sur les actes à accomplir auprès des offices de brevet des Etats contractants aux fins d'obtenir des droits dans les Etats contractants. Etant donné que les actes indispensables sont susceptibles de modifications, il serait bon de toujours consulter la dernière édition de la brochure. Toute information ultérieure est publiée au Journal Officiel.
2. **Traduction du fascicule du brevet européen en vertu de l'article 65(1) de la Convention sur le brevet européen**
Votre attention est de nouveau attirée sur l'obligation faite par certains Etats contractants, en vertu de l'article 65(1) CBE, de fournir une traduction du fascicule du brevet européen, à laquelle il est fait référence dans la notification établie conformément à la règle 71(5) CBE. Si la(les) traduction(s) n'est(ne sont) pas fournie(s), le brevet européen peut, dès l'origine, être réputé sans effet dans cet(ces) Etat(s). Pour plus de détails, nous vous renvoyons à la brochure susmentionnée.
3. **Paiement des taxes annuelles pour le brevet européen**
Conformément à l'article 141 CBE des taxes annuelles "nationales" dues au titre du brevet européen peuvent être perçues pour les années suivant celle au cours de laquelle la mention de la délivrance du brevet européen est publiée au "Bulletin européen des brevets". Pour plus de détails, nous vous renvoyons à la brochure susmentionnée.



European Patent Office
Postbus 5818
2280 HV Rijswijk
NETHERLANDS
Tel: +31 70 340 2040
Fax: +31 70 340 3016



Taravella, Brigitte
Sanofi
174, avenue de France
FR-75013 Paris
FRANCE

Formalities Officer
Name: Finger, Gabriela
Tel: +31 70 340 - 3260
or call
+31 (0)70 340 45 00

Application No. 09 744 185.1 - 1455	Ref. FR2009/028	Date 08.03.2013
Applicant SANOFI		

Communication under Rule 71(3) EPC

1. Intention to grant

You are informed that the Examining Division intends to grant a European patent on the basis of the above application with the text and drawings and the related bibliographic data as indicated below.

A copy of the relevant documents is enclosed.

1.1 In the text for the Contracting States:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO
SE SI SK SM TR

Description, Pages

1, 2, 4-18	as published		
3, 3a	received on	29-06-2012 with letter of	21-06-2012

Claims, Numbers

1-15	received on	29-06-2012 with letter of	21-06-2012
------	-------------	---------------------------	------------

Drawings, Sheets

1/1	as published
-----	--------------

With the following amendments to the above-mentioned documents proposed by the division

Description, Pages	1, 3-6, 9-11, 13-16
--------------------	---------------------

Claims, Numbers	3, 5, 12
-----------------	----------

Comments

Pages 1, 3-6, 9, 11, 13-16 adaptation of the description to the claims (Art. 84 EPC)

Page 10 - deletion of irrelevant matter/"spirit of invention" (Art. 84 EPC)

Claims 3 and 12 - improve legibility of claims to the printer

Claim 5 - correction of obvious orthographic error (missing comma)

1.2 Bibliographic data

The title of the invention in the three official languages of the European Patent Office, the international patent classification, the designated Contracting States, the registered name(s) of the applicant(s) and the other bibliographic data are shown on **enclosed EPO Form 2056**.

2. Invitation

You are invited, **within a non-extendable period of four months** of notification of this communication,

2.1 to EITHER approve the text communicated above and verify the bibliographic data (R. 71(5) EPC)

(1) by filing a translation of the claim(s) in the two other official languages of the EPO

Fee code	EUR
----------	-----

(2a) by paying the fee for grant including the fee
for publication:
minus any amount already paid (R. 71a(5) EPC):

007	875.00
	0.00

Total amount:	875.00
---------------	--------

(3) by paying additional claims fees under Rule 71(4) EPC;
number of claims fees payable: 0
minus any amount already paid (R. 71a(5) EPC):

016	0.00
	0.00

Total amount:	0.00
---------------	------

Note 1: See "Important notes concerning fee payments" below.

Note 2: Any overpaid "minus" amounts will be refunded when the decision to grant (EPO Form 2006A) has been issued.

2.2 OR, in case of disapproval, to request reasoned amendments or corrections to the text communicated above or keep to the latest text submitted by you (R. 71(6) EPC).

In this case the claims translations and fee payments mentioned under point 2.1 above are NOT due.

The terms "amendment(s)" and "correction(s)" refer only to amendments or corrections of the application documents and not of other documents (e.g. bibliographic data, the designation of the inventor, etc.).

If filing amendments, you must identify them and indicate the basis for them in the application as filed. Failure to meet either requirement may lead to a communication from the Examining Division requesting that you correct this deficiency (R. 137(4) EPC).

2.3 Bibliographic data

Where the applicant requests a change or correction of bibliographic data in response to the Rule 71(3) communication, this will **not** cause the sending of a second communication under Rule 71(3) EPC. The applicant will still have to pay the fees and file translations in reply to the Rule 71(3) communication in case of 2.1 above, unless he also files a reasoned request for amendments or corrections in response to the Rule 71(3) communication (see case 2.2 above).

3. Loss of rights

If either of the two possible actions above (see points 2.1 or 2.2) is not performed in due time, the European patent application shall be deemed to be withdrawn (R. 71(7) EPC).

4. Further procedure

4.1 In case of point 2.1 above

- 4.1.1 The decision to grant the European patent shall be issued, and the **mention of the grant** of the patent shall be published in the European Patent Bulletin, if the requirements concerning the translation of the claims and the payment of all fees are fulfilled and there is agreement as to the text to be granted (R. 71a(1) EPC).

Note on payment of the renewal fee:

If a renewal fee becomes due before the next possible date for publication of the mention of the grant of the European patent, publication will be effected only after the renewal fee and any additional fee have been paid (R. 71a(4) EPC).

Under Article 86(2) EPC, the obligation to pay renewal fees to the European Patent Office terminates with the payment of the renewal fee due in respect of the year in which the mention of the grant of the European patent is published.

Note on payment of the designation fee(s):

If the designation fee(s) become(s) due after the communication under Rule 71(3) EPC, the mention of the grant of the European patent shall not be published until the designation fee(s) has/have been paid (R. 71a(3) EPC).

- 4.1.2 After publication, the **European patent specification** can be downloaded free of charge from the EPO publication server <https://data.epo.org/publication-server> or ordered from the Vienna sub-office upon payment of a fee (OJ EPO 2005, 126).

Upon request in writing each proprietor will receive the certificate for the European patent together with one copy of the patent specification provided that the request is filed within the time limit of Rule 71(3) EPC. If such request has been previously filed, it has to be confirmed within the time limit of Rule 71(3) EPC. The requested copy is free of charge. If the request is filed after expiry of the Rule 71(3) time limit, the certificate will be delivered without a copy of the patent specification (R. 74 EPC, Decision of the President of the EPO, Special edition No. 3, OJ EPO 2007, D.2).

4.1.3 Filing of translations in the Contracting States

As regards translation requirements prescribed by the Contracting States under Article 65(1) EPC, please consult the website of the European Patent Office

www.epo.org → Law & practice → All Legal texts → National law relating to the EPC

www.epo.org → Law & practice → All Legal texts → London Agreement

In case of a valid extension

As regards translation requirements prescribed by the Extension States, please consult the website of the European Patent Office

www.epo.org → Law & practice → All Legal texts → National law relating to the EPC

Failure to supply a prescribed translation in a Contracting State or an Extension State may result in the patent being deemed to be void *ab initio* in the State concerned (Art. 65(3) EPC).

4.2 In case of 2.2 above

If the present communication under Rule 71(3) EPC is based upon an auxiliary request, and within the time limit you maintain the main or higher ranking request which is not allowable, the application will be refused (Art. 97(2) EPC).

If the Examining Division gives its consent to the requested amendments or corrections, it shall issue a new communication under Rule 71(3) EPC; otherwise, it shall resume the examination proceedings (R. 71(6) EPC).

5. Filing of a divisional application

Any divisional application relating to this European patent application must be filed directly with the European Patent Office in Munich, The Hague or Berlin and shall be in the language of the proceedings for the present application, or if the latter was not in an official language of the EPO, the divisional application may be filed in the language of the present application as filed (cf. Art. 76(1) and R. 36(2) EPC). Any such divisional application must be filed while the present application is still pending and the time limit for filing divisional applications must be observed (R. 36(1) EPC; Guidelines A-IV, 1.1.1).

The notification of this communication starts the 24-month period according to Rule 36(1)(a) EPC for filing a voluntary divisional application divided from this application or from any sequential application. For further information see Guidelines for Examination, A-IV, 1.1.1.2 and 1.1.1.4.

6. Important notes concerning fees payments

6.1 For all payments you are requested to refer to the relevant **fee code(s)**.

6.2 Automatic debiting procedure

The fee for grant including the fee for publication and any additional claims fees due under Rule 71(4) EPC will be debited automatically on the date of filing of the translations of the claims, or on the last day of the period of this communication. However, if the designation fee(s) become(s) due as set out in Rule 71a(3) EPC and/or a renewal fee becomes due as set out in Rule 71a(4) EPC, these should be paid separately by another permitted way of payment in order not to delay the publication of the mention of the grant. The same applies in these circumstances to the payment of extension fees. For further details see the Arrangements for the automatic debiting procedure (AAD) and accompanying information from the EPO concerning the automatic debiting procedure (Annexes A.1 and A.2 to the Arrangements for deposit accounts (ADA) in Supplement to OJ EPO 3/2009).

6.3 Fee amounts

Following any amendment to the Rules relating to Fees, the amount(s) mentioned in this communication may be different from the amount(s) **actually due on the date of payment**. The latest version of the Schedule of fees and expenses, published as a Supplement to the Official Journal of the EPO, is also available on the EPO website (www.epo.org) and can be found under www.epo.org/schedule-of-fees, which allows the viewing, downloading and searching for individual fee amounts, both current and previous.

6.4 Payments by cheque delivered or sent direct to the EPO are no longer accepted as from 1 April 2008 (see OJ EPO 2007, 626).

Examining Division:

Chairman:	Dudás, Eszter
2nd Examiner:	Konter, Jörg
1st Examiner:	Palma, Vera



Finger, Gabriela

For the Examining Division

Tel. No.: +31 70 340 - 3260

Branch at The Hague

Enclosure(s): 22 Copies of the relevant documents

EPO Form 2056



Europäisches
Patentamt
European
Patent Office
Office européen
des brevets

European Patent Office
Postbus 5818
2280 HV Rijswijk
NETHERLANDS
Tel: +31 70 340 2040
Fax: +31 70 340 3016

Application No.:

09 744 185.1

IV.2. Patent classification

The classification indicated on the published patent application remains unchanged. It is as follows:

INV. A61K9/20 A61K9/50 A61K31/4178 A61K31/4422 A61P9/12

IV.3. Title of the invention

The title indicated on the published patent application remains unchanged. It reads as follows:

FESTE PHARMAZEUTISCHE ZUSAMMENSETZUNGEN IN FIXER DOSISFORM
MIT IRBESARTAN UND AMLODIPIN, IHRE ZUBEREITUNG UND
THERAPEUTISCHE ANWENDUNG

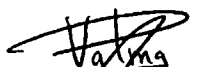
SOLID PHARMACEUTICAL FIXED DOSE COMPOSITIONS COMPRISING
IRBESARTAN AND AMLODIPINE, THEIR PREPARATION AND THEIR
THERAPEUTIC APPLICATION

COMPOSITIONS À DOSE PHARMACEUTIQUE SOLIDE FIXE COMPRENANT DE
L'IRBÉSARTAN ET DE L'AMLODIPINE, LEUR PRÉPARATION ET LEUR
APPLICATION THÉRAPEUTIQUE

IV.4. Documentation

27.02.2013.
Date


Dudás, Eszter
Chairman


Palma, Vera
1st examiner


Kontler, Jörg
2nd examiner

Enclosure(s):

~~SOLID PHARMACEUTICAL FIXED DOSE COMPOSITIONS COMBINING IRBESARTAN AND
AMLODIPINE, THEIR PREPARATION AND THEIR THERAPEUTIC APPLICATION~~

5 FIELD OF THE INVENTION

The present invention is directed to solid stable pharmaceutical fixed dose compositions comprising irbesartan, amlodipine besilate and pharmaceutically acceptable excipients, to their preparation and to their therapeutic application. <①>

10 BACKGROUND OF THE INVENTION.

Amlodipine is a calcium channel blocker developed for the treatment of hypertension and other medical indications as disclosed in USP 4,572,909 and USP 4,879,303. Its chemical name is 3-ethyl-5-methyl-(+)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methylpyridine-3,5-dicarboxylate.

15 Amlodipine is marketed as the monobenzenesulfonate salt, amlodipine besylate under the trade name Norvasc® or Istin®. It is available as oral tablets in strengths of 2.5 mg, 5 mg and 10 mg. The inactive ingredients in the Norvasc® tablets include microcrystalline cellulose, dibasic calcium phosphate anhydrous, sodium starch glycolate and magnesium stearate.

20 Amlodipine besylate is slightly soluble in water and has an absolute bioavailability of 64-90%.

Irbesartan is described in Bernhart et al., U.S. Patent No. 5,270,317, incorporated herein by reference.

25 Irbesartan, is a potent, long-acting angiotensin II receptor antagonist which is particularly useful in the treatment of cardiovascular ailments such as hypertension and heart failure. Its chemical name is 2-n-butyl-4-spirocyclopentane-1-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]-2-imidazolin-5-one.

Irbesartan is marketed by under the trade name Aprovel® or Karvea®.

30 Irbesartan is insoluble in water. Irbesartan has a parabolic pH solubility profile in aqueous medium with minimum solubility between pH 2.0 and 6.0 and maximum solubility in 0.1 N HCl and pH 7.5 phosphate buffer.

It is often desirable to combine multiple active ingredients in a single pharmaceutical composition. Inclusion of multiple ingredients in a single composition generally reduces costs and provides the convenience of consuming a single medication rather than multiple medications for treating individual symptoms.

35 However, a combination of active ingredients is not without drawbacks.

① according to claim 1

Certain physical properties of the drugs and specifically stability, present a challenge in developing formulations suitable for preparing a tablet having reduced levels of total impurities on long term stability.

Irbesartan is, for example, a fluffy material, with relatively low bulk and tap densities. It is also a sticky and abrasive material .

These properties make it difficult to formulate an effective amount of the drug into a small tablet with uniformity of weight, hardness, and other desirable tablet properties. In addition, irbesartan has certain undesirable flow characteristics, for example, is sticky and can adhere to surfaces such as tablet punch faces and dies, causing problems in tableting, especially on a high speed tablet press.

The very low aqueous solubility of irbesartan also presents a challenge, since only limited amounts of excipients may be added to facilitate wetting, disintegration, and ultimately, rapid and complete drug release.

The addition of a second active ingredient such as amlodipine besilate, which is also a fluffy material exhibiting poor flow and low aqueous solubility, can further contribute to problems such as tableting or uniformity of dosage units.

In addition, the stability of a composition might be compromised due to incompatibility of an active with an essential excipient or even between a second active itself.

Concerning formulations containing Amlodipine besilate alone, WO 2006/059217 discloses that amlodipine is highly hygroscopic and absorbs moisture, which leads to degradation. One of the major routes of degradation is via a catalytic oxidative process, which is pH dependent. One of the major degradation products known in the art is 3-ethyl-5-methyl-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methylpyridine-3,5-dicarboxylate and called Impurity D.

WO2003/051364 discloses Amlodipine besilate tablets with improved stability of the active ingredient and reduced in weight containing microcrystalline cellulose, a lubricant and a disintegrating agent and the process for the preparation of said tablets.

WO2008/062435 discloses a stable solid dosage form of amlodipine besilate comprising polyols and having reduced levels of total impurities on stability and especially impurity D.

Concerning formulations containing Irbesartan, EP747050 from Sanofi discloses pharmaceutical composition under tablets comprising Irbesartan alone or in combination with a diuretic compound such as Hydrochlorothiazide (HCTZ) prepared by a process comprising mixing an extragranular composition with granules comprising either irbesartan alone or the two active principles in the presence of lactose and an antiadherent such as silicon dioxide. No problem of stability is raised.

WO2005/070762 from Sepracor discloses oral formulation under capsules comprising the combination of S-amlodipine and Irbesartan obtained by simple mixing about 25wt% of the two active principles together in the presence of corn starch and about 65wt% of lactose. No problem of stability is raised.

5 WO2008/044862 discloses a combined multi-layered tablet containing amlodipine maleate delayed-immediate-release granules and irbesartan immediate-release layer granules for enabling the two drugs to be chronotherapeutically released, thereby improving the therapeutic activity while reducing side effects. However, such combination is not stable and a high impurity D level appears over the time.

10 Thus, there is no known stable solid dosage form comprising the specific combination of Irbesartan and Amlodipine besilate.

In addition to stability, when formulating solid fixed dose combination, the objective is to provide a patient-convenient combination dosage form of active ingredients that is bioequivalent to the corresponding free-combination of the same active ingredients.

15 As used herein, "fixed-dose-combination or FDC" refers to a combination of two drugs or active ingredients presented in a single dosage unit such as a tablet or oral dosage form.

Further as used herein, "free- combination" refers to a combination of two drugs or active ingredients dosed simultaneously but as two dosage units.

20 As a result of these complex biopharmaceutical properties, development of a fixed-combination dosage form of irbesartan and amlodipine besilate that is bioequivalent to a free-combination thereof is challenging.

Accordingly, a fixed-combination solid dosage formulation of Irbesartan and amlodipine besilate that is stable and bioequivalent to the corresponding free-combination would be desirable.

25 One other challenge faced is homogeneity of Amlodipine in a lubricated blend as the content of Amlodipine in the total tablet weight should be very low compared to the high amount of irbesartan.

30 The object of the present invention is to alleviate at least partly the above mentioned drawbacks.

SUMMARY OF THE INVENTION

35 This object is achieved with a stable solid oral pharmaceutical fixed dose composition comprising irbesartan, amlodipine besilate and pharmaceutically acceptable excipients, wherein irbesartan is physically separated from amlodipine besilate.

① according to claim 1

→ p. 3a

29/06/2012

→ 3a

This solid dosage form is particularly advantageous since amlodipine besilate does not undergo degradation and this combination product shows reduced and controlled impurities even lesser than with regards to individual reference products of same dose when subjected to stress studies and in finished pack.

5

4.

In addition, the dissolution profile of both irbesartan and amlodipine besilate is not compromised by comparison to the dissolution profile of each active ingredient alone.

~~In a preferred embodiment,~~ Irbesartan under the form of coated granules is
5 embedded in an extragranular matrix comprising amlodipine besilate.

~~Preferably,~~ The solid composition of the invention takes the form of a monolayer tablet, preferably film coated.

Preferably, the tablet is further package in suitable packing material such as PVC, PVC / PVdC, PVC / PE / PVdC.

10 In a preferred embodiment of the composition according to invention, the irbesartan represents between about 20% and about 70% by weight of the total composition.

In a preferred embodiment of the composition according to invention the amlodipine besilate represents between about 1% and about 20% by weight of the
15 total composition.

In a preferred embodiment of the composition according to invention the pharmaceutically acceptable excipients are selected from the group consisting of diluent, disintegrant, antiadherent, binder lubricant and mixture thereof.

Preferably said solid composition is free of lactose.

20 In a preferred embodiment of the composition according to invention the amount of Irbesartan is comprised between 150mg and 300mg of the total weight of the tablet, preferably 300mg or 150mg.

In a preferred embodiment of the composition according to invention the amount of amlodipine besilate is comprised between 5mg and 10mg of the total
25 weight of the tablet, preferably 7mg or 14mg.

In a preferred embodiment of the composition according to invention the solid composition is under the form of a tablet wherein the total weight of the tablet is between 400mg and 600mg, preferably 500mg.

30 In a preferred embodiment the composition has less than 1.50%(w/w) of total impurities for Amlodipine and less than 0.50%(w/w) of total impurities for Irbesartan after 6 months at 40°C/75%RH.

According to another object, the invention is related to a process for the preparation of a stable oral pharmaceutical composition comprising irbesartan and amlodipine besilate, wherein the process comprises the steps of:

① in a form of a monolayer tablet

- 5
- i. granulating irbesartan and one or more pharmaceutically acceptable excipients, with aqueous solution containing a binder, to form granules,
 - ii. drying the granules;
 - iii. separately blending amlodipine besilate with pharmaceutically acceptable excipients,
 - iv. mixing the irbesartan granules of step ii with the amlodipine besilate blend of step iii);
 - v. lubricating the blend of step iv); optionally after a pre-lubricating step; and
 - vi. compressing the mixture into tablets.

10 Preferably, the group of pharmaceutically acceptable excipients used in step I and iii) of the process is free of lactose.

In a preferred embodiment of the process further comprises the step of coating the tablet and packaging in suitable packing material such as PVC, PVC / PVdC, PVC / PE / PVdC.

15 Preferably the pre-lubricating step comprises the mixing of the blend of step (iv) during 10 to 25mn, preferably 20mn before doing the lubricating step.

20 According to another object, the invention is related to the use of Irbesartan and amlodipine besilate in the manufacture of a medicament for the treatment of hypertension wherein said medicament is in the stable solid fixed dose composition as described above.

Preferably, the use referred to a second line treatment for hypertensive patients not sufficiently controlled using amlodipine as Calcium Channel Blockers (CCB) monotherapy or irbesartan as angiotensin II receptor antagonist (ARB).

25 BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows the dissolution profile of Irbesartan in routine media i.e. 0.1 N HCl.

Fig 2 shows the dissolution profile of amlodipine in routine media i.e. 0.1 N HCl.

30 DETAILED DESCRIPTION OF THE INVENTION.

Preferred Irbesartan and Amlodipine besilate compositions.

The two actives are present in a single unit dosage form, ~~such as~~ tablets or ~~pellets~~, wherein irbesartan is physically separated from amlodipine besilate.

Pharmaceutically acceptable additives suitable for use in the present invention with amlodipine besylate are selected from suitable diluents such as microcrystalline cellulose, di calcium phosphate and suitable lubricants such as magnesium stearate.

Pharmaceutically acceptable additives suitable for use in the present invention with Irbesartan are selected from suitable diluents such as Microcrystalline cellulose, suitable glidants such as silicone dioxide, suitable lubricants such as magnesium stearate, suitable binders such as hypromellose.

In the composition of the invention, Amlodipine portion composition is similar to the reference composition of Amlodipine formulation Norvasc® and Irbesartan portion is similar to the reference composition of Aprovel® except without Lactose monohydrate.

In a preferred embodiment, the composition is free of lactose as diluent. Indeed the absence of this excipient allows achieving best results in term of global stability of amlodipine besilate and specifically lowering the amount of impurity D.

~~In a preferred form of the tablet~~ Irbesartan is present under the form of coated granules embedded in an extragranular matrix comprising amlodipine besilate along with excipients. Irbesartan is granuled with a binder such as HPMC for facilitating granulation and amlodipine is added in the extragranular portion before compression step.

~~In another preferred form, irbesartan and amlodipine are both separately granulated using respective suitable binder before blending with lubricants and further compression.~~

Thus the solid composition takes the form of a monolayer tablet, preferably film coated.

~~In another preferred form, irbesartan granules and amlodipine granules along with excipients are separated by an inert layer. Thus the solid composition takes the form of a trilayer tablet, preferably film coated. In that embodiment the inert layer preferably comprises suitable diluent.~~

The ~~preferred~~ form is a monolayer form wherein a physical barrier is placed around the irbesartan active ingredient. The physical barrier serves to reduce or eliminate the physical contact between irbesartan as the protected active ingredient and amlodipine besilate, the other active ingredient of the combination.

Preferred compositions of the present invention contain one or more of the following components in the indicated concentration range (% by weight): irbesartan, 50 to 70% most preferably, 60%, amlodipine besilate, 1 to 10%, most preferably 2 to 6%, diluent, 20 to 30%, most preferably about 25%, binder, 1 to 5%, most preferably

2 to 3%; disintegrant, 3 to 6%, most preferably about 5%; antiadherent or glidant, 0.25 to 5.0% most preferably 0.7 to 2%, lubricant, 0.5 to 1.5, most preferably about 1%.

The amount of each ingredient (active and additives) in the solid dosage formulation of the invention may specifically vary within the following ranges.

5

.	Component	Total % Content in the formulation			
		150 / 5 mg strength	150 / 10 mg strength	300 / 5 mg strength	300 / 10 mg strength
Intragranular					
1	Irbesartan	60.00	60.00	60.00	60.00
2	Diluent	26.40	21.60	26.40	26.40
3	disintegrant	4.80	4.80	480	4.80
4	binder	2.00	2.00	2.00	2.00
5	Purified water	q.s.	q.s.	q.s.	q.s.
Extragranular					
6	Amlodipine Besilate equivalent to Amlodipine	2.80	5.60	1.40	2.80
7	diluent	2.00	4.00	3.40	2.00
8	Antiadherent or glidant	1.00	1.00	1.00	1.00
9	lubricant	1.00	1.00	1.00	1.00
10	Coating material	4.00	4.00	4.00	4.00

Particle size distribution of Irbesartan is important because the fines of Irbesartan granules help for uniformity of Amlodipine. The particle size distribution of Irbesartan granules mainly depends on fluid uptake during granulation and kneading time. The preferred size distribution of Irbesartan granules is in the range of 65 to 85% passing through # 60 BSS, i.e. having a size or a diameter less than 250µm.

The final pH observed for the Irbesartan and Amlodipine formula composition of the invention is around 6.0, where as pH of individual reference product was found to be higher than 6.0 i.e. in between pH 6.0 to 7.0. The Amlodipine composition favors pH above 6, but below pH 6.0 the degradation process of amlodipine accelerates.

Hence in the present invention the selected compositions can attain pH 6 when compressed into tablets.

The final primary packaging material used is blister packaging i.e. Opaque Triplex (300micPVC/30micPE/90gsmPVdC), Opaque duplex (250micPVC and 60 mic PVdC) and Alu-Alu blister packs. These materials will avoid increasing generation of Impurity-D in amlodipine thereby inhibiting direct exposure of sun light on drug product.

The main impurity to be controlled in the composition of the invention is Impurity D known in the art as 3-ethyl-5-methyl-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methylpyridine-3,5-dicarboxylate.

In the compositions according to the invention, less than 1.5 % (w/w) of total impurities for Amlodipine is found after 6 months at 40°C/75%RH, but more than 1.6% of impurity is found when irbesartan and amlodipine are not physically separated. In a preferred embodiment less than 1,0% and more preferably less than 0,5% (w/w) of total impurities for Amlodipine is found in the composition of the invention after 6 months at 40°C/75%RH.

In addition less than 1,5%(w/w) [actual 0.097 % w/w] of Impurity D for Amlodipine is found after 6 months at 40°C/75%RH in the compositions according to the invention, but more than 1,6% of impurity D is found when Irbesartan and amlodipine are not physically separated. In a preferred embodiment less than 1,0% and more preferably less than 0,15% (w/w) of impurity D for Amlodipine is found in the composition of the invention after 6 months at 40°C/75%RH.

This shows that the specific compositions of the invention have a lowering impact on the degradation profile of amlodipine besilate.

On the other side less than 0,5 % (w/w) of total impurities for irbesartan is found after 6 months at 40°C/75%RH. This shows that the specific composition of the invention have no impact on the degradation profile of Irbesartan. In addition, there is no change in the physical properties of tablets such as color, shape, hardness, and disintegration time.

Physical properties.

Stability performances.

The oral pharmaceutical compositions of the present invention were subjected to accelerated stability studies at the following conditions; 40°C/ 75 % relative humidity RH, 30°C / 75 % RH and 25°C/ 60 % RH. These were evaluated on the basis of assay, in vitro dissolution, moisture content and related substances measured between initial and 6-months time points for irbesartan as well as amlodipine besilate.

The results provide a significant decrease in the total impurity levels in Amlodipine mainly Imp D when Irbesartan and Amlodipine both are physically separated.

Specifically, it was found that impurity levels in the Amlodipine is quite low and within the target limit in the formula where Irbesartan granulated and Amlodipine was added in the extragranular portion. This composition shows impurity levels much lower than that of reference products.

Dissolution performances.

The "dissolution performance" of a tablet containing the combination of Irbesartan and amlodipine besilate is compared to the dissolution performance of each reference product in multimedia dissolution conditions such as 0.1 N HCl, pH 4.5
5 Acetate buffer, pH 6.8 phosphate buffer and pH 7.5 phosphate buffer. The progress of dissolution is monitored at various time points between initial point and 60 minutes.

The dissolution profiles refers to the weight % of irbesartan or amlodipine release, based on the total weight of irbesartan or amlodipine contained in the tablet, which dissolves within 60 minutes under the different multimedia conditions (see fig 1
10 and 2 for routine media i.e. 0.1 N HCl).

The results show that the dissolution performances of the tablet containing the combination of irbesartan and amlodipine besilate of the invention are equivalent to the dissolution performances of the tablets containing each active ingredient irbesartan or amlodipine alone.
15

Method of manufacture.

The process for the preparation of a stable oral pharmaceutical composition $\langle \textcircled{1} \rangle$ comprising irbesartan and amlodipine besilate, comprises the following steps:

i. granulating irbesartan and one or more pharmaceutically acceptable
20 excipients with aqueous solution containing a binder to form granules,

Preferably acceptable excipients are selected from the group consisting of microcrystalline cellulose, croscarmellose sodium. Preferably acceptable binder, are selected from the group consisting of cellulose derivatives such as hydroxypropyl methylcellulose.

25 ii. drying the granules;

iii. separately blending amlodipine besilate with pharmaceutically acceptable excipients for better uniform distribution of Amlodipine. Preferably acceptable excipients are selected from the group consisting of microcrystalline cellulose, silicon dioxide.

30 iv. mixing the irbesartan granules of step i) with the amlodipine besilate blend of step iii);

v. lubricating the blend of step iv); optionally after a pre-lubricating step;
and

vi. compressing the mixture into tablets.

35 In a preferred embodiment of the process, a pre-lubricating step is carried on before step v) in order to achieve good homogeneity for both Irbesartan and

$\textcircled{1}$ in a form of a monolayer tablet

Amlodipine. Preferably the pre-lubricating step comprises the mixing of the blend of step (iv) during 10 to 25mn, preferably 20mn before doing the lubricating step.

Indeed, since the Irbesartan is present in the intragranular portion and Amlodipine is mixed with other extragranular excipients like Microcrystalline Cellulose and silicon dioxide, homogeneous distribution of Amlodipine in the final blend is necessary.

Hence, proper mixing of intragranular and extragranular material is important stage to achieve homogeneity of Amlodipine in the final blend, which can be done during prelubrication step by mixing Irbesartan granules with extragranular material till the content uniformity for Amlodipine is achieved, between 90 to 110% of the label claim with RSD (Relative standard deviation) less than 5%, which revealed the uniform distribution of Amlodipine Besilate in the lubricated blend.

In a preferred embodiment, the group of pharmaceutically acceptable excipients used in the process is free of lactose.

The process further comprises the step of coating the tablet and packaging preferably in opaque triplex blister pack.

Efficacy performance.

An object of the invention is the use of the composition of the invention containing Irbesartan and amlodipine besilate in the manufacture of a medicament for the treatment of hypertension wherein said medicament is in stable solid fixed dose compositions as described above.

In a preferred embodiment, the compositions of the invention are administered to patient having a mild to moderate hypertension, as second line treatment for hypertensive patients not sufficiently controlled on amlodipine (Calcium Channel Blockers CCB) or irbesartan (angiotensin II receptor antagonist ARB) monotherapy.

Phase III, double-blind, randomized, placebo-controlled, 8-week partial factorial was designed to evaluate the combinations of Irbesartan 150 mg / Amlodipine 5 mg and Irbesartan 300 mg / Amlodipine 5 mg tablets versus Amlodipine 5 mg, Irbesartan 150 mg and 300 mg monotherapy, after 8 weeks of treatment in patients with uncomplicated primary essential hypertension.

This study aims to demonstrate that the antihypertensive efficacy of the fixed dose composition Irbesartan and amlodipine 150/5mg or 300/5mg is superior to the corresponding dose of monotherapy of amlodipine or irbesartan.

~~The invention has been described with reference to preferred embodiments. However, many variations are possible within the scope of the invention.~~

Examples.

C1, C2, C3 represent comparative formulations. I1 ~~I2, I3 represent formulations~~ / <①>
of the invention wherein irbesartan is physically separated from amlodipine. / <②>

Aprovel® 300mg Karvea® 300mg represents formula C1 as reference product
5 for Irbesartan alone.

Istin 10mg or Norvasc® 10mg represents formula C2 as reference product for
Amlodipine besilate alone.

Comparative ^{le} Example 1.

10 Preparation of composition C3 wherein Irbesartan and Amlodipine are both
granulated together.

Table 1

Name of ingredients	Quantity (mg/tab)
Intragranular Phase	
Irbesartan	300.00
Amlodipine Besilate	14.00
Microcrystalline Cellulose	142.00
Croscarmellose Sodium	24.00
Hypromellose	10.00
Purified Water #	q.s
Extra granular Phase	
Colloidal Silicon Dioxide	5.00
Magnesium Stearate	5.00
Total weight of core tablet (mg)	500.00
Opadry white II	10.00
Total weight of coated tablet (mg)	510.00

15 This formula C3 may be prepared by any suitable granulation process known in
the art.

Example 2.

20 Preparation of composition of the invention I1 wherein Irbesartan is in the
Intragranular portion and Amlodipine is added in the extragranularly

① represents a formulation

② I2 and I3 represent reference formulations wherein irbesartan
is physically separated from amlodipine.

This combination is also referenced under Test product.

Table 2

Step. No.	Component	Function	(%)	Quantity / unit (mg)	
			Qty / unit	150mg/5mg	300mg/10mg
Internal Phase					
1.	Irbesartan	Active substance	60.00	150.00	300.00
2.	Microcrystalline Cellulose (Avicel PH 101)	Diluent/Binder	26.40	66.00	132.00
3.	Croscarmellose sodium	Disintegrant	4.80	12.00	24.00
4.	Hypromellose (HPMC 6 cps)	Binder	2.00	5.00	10.00
5.	Purified water ^a	Solvent for granulation	q.s.	q.s.	q.s.
External Phase					
6.	Amlodipine Besylate equivalent to Amlodipine	Active substance	2.80	7.00 5.00	14.00 10.00
7.	Microcrystalline Cellulose (Avicel PH 112)	Diluent	2.00	5.00	10.00
8.	silicon dioxide	Glidant/antiadherent	1.00	2.50	5.00
9.	Magnesium stearate	Lubricant	1.00	2.50	5.00
Core Tablet Weight			100 %	250 mg	500 mg
10.	Opadry White 03B28796 ^b	Coating agent	4.00	10.00	20.00
11.	Purified water ^a	Solvent for coating	q.s.	q.s.	q.s.
Coated Tablet Weight				260 mg	520 mg

5 Extragranulation process of manufacturing the combination of Irbesartan and amlodipine besilate under tablet according to formula II.

Step -1: Mix Irbesartan, Microcrystalline cellulose and Croscarmellose sodium in raped mixer granulator.

Step-2: Granulate the dry mix of step 1 with aqueous solution of hypromellose.

Step- 3: Dry the wet granules and mill the dried granules through 1.00 to 2.00 mm screen.

Step- 4: Add extragranular material i.e. Amlodipine Besilate, Microcrystalline Cellulose and Silicone dioxide and mix in a low shear blender.

5 Step- 5: Add Magnesium Stearate to step 4 material and mix in a low shear blender.

Step- 6: Compress the lubricated blend using suitable toolings.

Step- 7: Finally coat the compressed tablets to achieve 2 – 4 % of weight gain.

Reference Example 3.

10 Preparation of composition of the invention I2 wherein Irbesartan and Amlodipine besilate are physically separated by both separate granulations.

Table 3

Step.No.	Name of ingredients	Quantity (mg/tab)
Irbesartan Granulation		
01	Irbesartan	300.00
02	Microcrystalline Cellulose	50.00
03	Croscarmellose Sodium	20.00
04	Hypromellose	7.00
05	Purified Water #	q.s
Amlodipine Besilate Granulation		
06	Amlodipine Besilate	14.00
07	Povidone K 30	9.00
08	Calcium Hydrogen Phosphate	60.00
09	Microcrystalline Cellulose	40.00
10	Crospovidone	6.00
11	Purified Water #	q.s
Extragranular Phase		
12	Microcrystalline Cellulose	10.00
13	Colloidal Silicon Dioxide	5.00
14	Magnesium Stearate	5.00
Total weight of core tablet (mg)		526.00
15	Opadry white II	10.00
Total weight of coated tablet (mg)		536.00

Reference ^{1e} Example 4.

Preparation of composition of the invention I3 under tri-layers tablet wherein Irbesartan layer and Amlodipine besilate layer are physically separated by an inert layer.

5 Table 4

Step .N°	INGREDIENTS	Qty / Tab (mg)
Irbesartan Layer – weight 500 mg		
1.	Irbesartan	300.0
2.	Lactose monohydrate	102.0
3.	Microcrystalline cellulose	54.0
4.	Croscarmellose sodium	24.0
5.	Hypromellose	10.0
6.	Purified water	qs
7.	Colloidal silicon dioxide	5.0
8.	Magnesium stearate	5.0
Inert layer – weight 200 mg		
9.	Microcrystalline cellulose	169.75
10.	Partially pregelatinized starch	30.0
11.	Iron oxide red (colorant)	0.25
Amlodipine layer – weight 220 mg		
12.	Amlodipine besilate	14.0
13.	Povidone k 30	20.0
14.	Microcrystalline cellulose	60.0
15.	Crospovidone	6.0
16.	Calcium hydrogen phosphate, anhydrous	106.0
17.	Purified water	Qs
18.	crospovidone	11.0
19.	Magnesium stearate	3.0
Average weight of the tablet		920 mg

Example 5.**Stability studies**

The oral pharmaceutical compositions of the present invention were subjected to accelerated stability studies at the following conditions; 40°C/ 75 % relative humidity
5 RH, 30°C / 75 % RH and 25°C/ 60 % RH. These were evaluated on the basis of assay, in vitro dissolution, moisture content and related substances measured between initial and 6-months time points for irbesartan as well as amlodipine besilate.

This test is carried on under the following conditions.

The tablets were packed in to the opaque triplex – alu blister pack and such
10 blister were further packed in to the cartons, and cartons were charged on to the stability as per ICH guidelines, and samples were taken out at each stability stage interval and submitted for analysis.

The stability results at +40°C/75%RH are provided in table 5.

Table 5

Ex.	Conditions	Total Impurities from irbesartan in %w/w of the total composition	Impurity-D from Amlodipine in %w/w of the total composition		Total Impurities from amlodipine in %w/w of the total composition.	
			initial	6 months	initial	6 months
C1	Irbesartan Aprovel 300mg	0,14	NA	NA	NA	NA
C2	Amlodipine besilate Test product Istin 10mg	NA	0,06	0,38	0,05	0,99
C3	Irbesartan + Amlodipine besilate COMBINED GRANULATION	0,15*	0,49*	1,60*	0,70*	2,33*
I1	Irbesartan + Amlodipine besilate SEPARATION by extragranulation Test product <①>	0,171	0,017	0,097	0,066	0,329
I2	Irbesartan + Amlodipine besilate SEPARATION by granulation<②>	0,08**	0,06**	0,16**	0,15**	0,33**
I3	Irbesartan + Amlodipine besilate SEPARATION by triple layer<②>	0,034**	0,026**	0,188**	0,046**	0,388**
* 2 months ** 3 months						

15

The formulation containing both Irbesartan and Amlodipine granulated together shows higher level of imp D during stability studies at 40°C / 75 % RH at 2 months, hence further stability study was discontinued.

① (according to the invention)

② (not according to the invention)

From the above results, it may be concluded that there is an increase in the total impurity levels in Amlodipine and mainly Imp D when Irbesartan and Amlodipine are granulated together.

When Irbesartan and Amlodipine both are physically separated it was found that impurity levels in the Amlodipine is quite low.

Hence formula II where Irbesartan granulated and Amlodipine was added in the extragranular portion shows the best results of impurity levels i.e. specifically much lower than that of reference products (Istin 10 mg).

In the compositions ~~according to the invention~~ I1, I2, I3, less than 1.5% (w/w) of total impurities for Amlodipine is found after 6 months at 40°C/75%RH, although more than 1.6% of impurity is found when irbesartan and amlodipine are not physically separated (C3). In a preferred embodiment less than 1.0% and more preferably less than 0.5% (w/w) of total impurities for Amlodipine is found in the composition ~~of the invention~~ (I1, I2, I3) after 6 months at 40°C/75%RH.

In addition less than 1.5% (w/w) of Impurity D for Amlodipine is found after 6 months at 40°C/75%RH in the compositions ~~according to the invention~~ (I1, I2, I3), although more than 1.6% of impurity D is found when irbesartan and amlodipine are not physically separated (C3). In preferred embodiments, less than 1.0% and more preferably less than 0.15% (w/w) of impurity D for Amlodipine is found in the composition ~~of the invention~~ (I1, I2, I3) after 6 months at 40°C/75%RH.

In a more preferred embodiment less than 0.15% (w/w) of impurity D for Amlodipine and less than 1.5 % (w/w) of total impurities for Amlodipine is found after 6 months at 40°C/75%RH in the composition of the invention (I1).

This shows that the specific compositions of the invention have a lowering impact on the degradation profile of amlodipine besilate.

On the other side less than 0.5 % (w/w) of total impurities for irbesartan is found after 6 months at 40°C/75%RH. This shows that the specific composition of the invention have no impact on the degradation profile of Irbesartan.

Example 4

Bioequivalence Dissolution profiles.

The dissolution profiles of the products of the invention are compared to the dissolution profiles of the reference products. These studies are carried out per the multimedia dissolution profile study conditions established as followed.

The dissolution profiles were carried out with avg tablet weight of 260 mg [for 150/5 mg & 150/10 mg] or 520 mg [for 300/5 & 300/10 mg strength] of Irbesartan and Amlodipine FCT using USP apparatus II, placing a tablet in 900 ml of dissolution

media at 37°C and measuring the amount of Irbesartan or Amlodipine progressively dissolved [using HPLC, wavelength 240 nm] at different time points such as 10, 15, 30, 45 & 60 mins till the extend of 90% drug dissolves was achieved.

The results as illustrated in figures 1 and 2 show that the dissolution performances of the tablet containing the combination of irbesartan and amlodipine besilate of the invention are equivalent to the dissolution performances of the tablets containing each active ingredient irbesartan or amlodipine alone.

Example 5.

10 Clinical studies Phase III.

The first study is conducted with the fixed combination of irbesartan and amlodipine 150/5 and 300/5mg and with irbesartan 150 and 300 mg.

The combination therapy of irbesartan and amlodipine is expected to provide enhanced efficacy in patients not adequately controlled by irbesartan monotherapy alone.

The second study is conducted with the fixed combination of irbesartan and amlodipine 150/5 and 150/10 mg and with amlodipine 5 and 10 mg.

The combination therapy of irbesartan and amlodipine is expected to provide enhanced efficacy in patients not adequately controlled by irbesartan monotherapy alone.

The results will demonstrate that the antihypertensive effect as assessed by home blood pressure measurement (HBPM) of the fixed combination of irbesartan and amlodipine 150/5 mg is superior to that of amlodipine 5 mg alone in hypertensive patients insufficiently controlled by amlodipine 5 mg monotherapy.

244 patients are randomised in each clinical study. This will give 122 patients randomised and 103 patients for evaluation in each treatment group.

All the treatments were administrated orally, once daily in the morning.

Efficacy criteria.

Home Blood pressure BP measurements is performed using for all patients the same validated automatic non invasive BP monitor according to a standard procedure: Twice a day for 7 days, 2 measurements in the morning and 2 measurements in the evening.

These HBPM periods are performed the week before V2, V3 and V4.

Office BP measurements are performed at each visit. All investigators are using the same validated automatic non invasive BP monitor.

Primary efficacy criterion: Home SBP as primary criterion is based on the measurements made by the patient for the last 7 days of each measurement period.

Morning and evening measurements of the first day of each measurement period are discounted in this criterion as they are considered as a training.

The primary criterion is calculated based on the average of all available measurements out of a maximum of 24 measurements (4 measurements per day for 6 days). This average is computed only if a minimum of 12 correct measurements are recorded over the last 6 days of each period of measurement.

From the first study, the results will demonstrate that the antihypertensive efficacy of the fixed combination irbesartan/amlodipine 300/5 mg is superior to that of irbesartan 300 mg monotherapy in lowering Systolic Blood Pressure assessed by home blood pressure measurement (HBPM) after 10 weeks of treatment (W10).

From the second study, the results will demonstrate that the antihypertensive effect as assessed by home blood pressure measurement (HBPM) of the fixed combination of irbesartan and amlodipine 150/5 mg is superior to that of amlodipine 5 mg alone in hypertensive patients insufficiently controlled by amlodipine 5 mg monotherapy.

CLAIMS

- 1) A stable solid oral pharmaceutical fixed dose composition in a form of a
5 monolayer tablet comprising irbesartan, amlodipine besilate and pharmaceutically
acceptable excipients, wherein irbesartan is physically separated from amlodipine
besilate and wherein irbesartan under the form of coated granules is embedded in an
extragranular matrix comprising amlodipine besilate.
- 2) The composition according to claim 1, wherein the tablet is film coated.
- 10 3) The composition according to any one of claims 1 to 2 wherein the irbesartan
represents between 20% and 70% by weight of the total composition.
- 4) The composition according to any one of claims 1 to 3 wherein the amlodipine
besilate represents between 1% and 20% by weight of the total composition.
- 15 5) The composition according to any one of claims 1 to 4 wherein the
pharmaceutically acceptable excipients are selected from the group consisting of
diluent, disintegrant, antiadherent, binder, lubricant and mixture thereof.
- 6) The composition according to any one of claims 1 to 5 wherein said solid
composition is free of lactose.
- 20 7) The solid composition according to any one of claims 1 to 6 wherein the
amount of Irbesartan is comprised between 150mg and 300mg of the total weight of
the tablet, preferably 300mg or 150mg.
- 8) The solid composition according to any one of claims 1 to 7 wherein the
amount of amlodipine besilate is comprised between 5mg and 10mg of the total
weight of the tablet, preferably 7mg or 14mg.
- 25 9) The solid composition according to any one of claims 1 to 8 under the form of
a tablet wherein the total weight of the tablet is between 400mg and 600mg,
preferably 500mg.
- 10) The composition according to any one of claims 1 to 9 having less than
1.50%(w/w) of total impurities for Amlodipine and less than 0.50%(w/w) of total
30 impurities for Irbesartan after 6 months at 40°C/75%RH.
- 11) A process for the preparation of a stable oral pharmaceutical composition in a
form of a monolayer tablet comprising irbesartan and amlodipine besilate, wherein the
process comprises the steps of:

- i. granulating irbesartan and one or more pharmaceutically acceptable excipients, with aqueous solution containing a binder, to form granules,
 - ii. drying the granules;
 - 5 iii. separately blending amlodipine besilate with pharmaceutically acceptable excipients,
 - iv. mixing the irbesartan granules of step ii with the amlodipine besilate blend of step iii);
 - v. lubricating the blend of step iv); optionally after a pre-lubricating step; and
 - vi. compressing the mixture into tablets.
- 10 12) The process of claim 11 wherein the group of pharmaceutically acceptable excipients used in step I and iii) of the process is free of lactose.
- 13) The process according to any one of claims 11 to 12 wherein the pre-lubricating step comprise the mixing of the blend of step (iv) during 10 to 25mn, preferably 20mn before doing the lubricating step.
- 15 14) Use of Irbesartan and amlodipine besilate in the manufacture of a medicament for the treatment of hypertension wherein said medicament is in the stable solid fixed dose composition according to anyone of claim 1 to 10.
- 15 15) Use according to claim 14 as second line treatment for hypertensive patients not sufficiently controlled using amlodipine as Calcium Chanel Blockers (CCB)
- 20 monotherapy or irbesartan as angiotensin II receptor.antagonist (ARB).

42

~~DRAWINGS~~

Figure 1

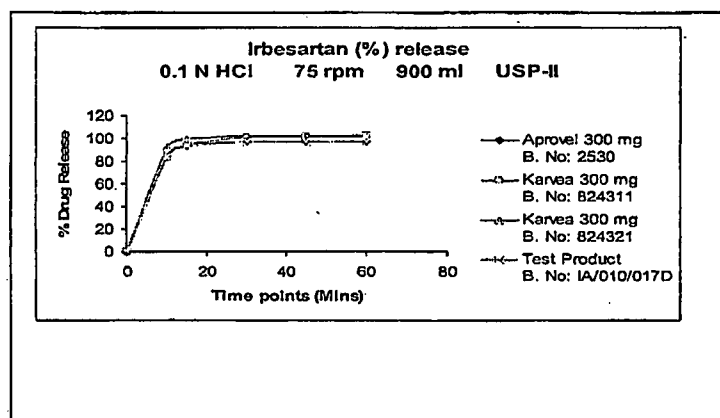
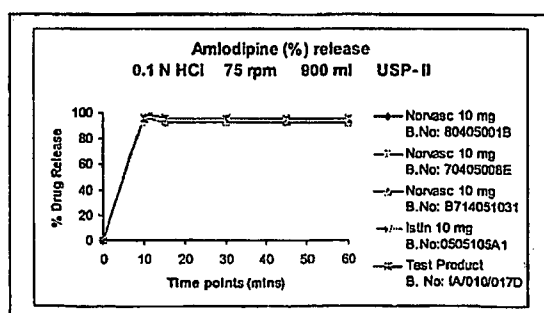


Figure 2



CLAIMS

- 5 1) A stable solid oral pharmaceutical fixed dose composition in a form of a monolayer tablet comprising irbesartan, amlodipine besilate and pharmaceutically acceptable excipients, wherein irbesartan is physically separated from amlodipine besilate and wherein irbesartan under the form of coated granules is embedded in an extragranular matrix comprising amlodipine besilate.
- 2) The composition according to claim 1, wherein the tablet is film coated.
- 10 3) The composition according to any one of claims 1 to 2 wherein the irbesartan represents between 20% and 70% by weight of the total composition.
- 4) The composition according to any one of claims 1 to 3 wherein the amlodipine besilate represents between 1% and 20% by weight of the total composition.
- 15 5) The composition according to any one of claims 1 to 4 wherein the pharmaceutically acceptable excipients are selected from the group consisting of diluent, disintegrant, antiadherent, binder lubricant and mixture thereof.
- 6) The composition according to any one of claims 1 to 5 wherein said solid composition is free of lactose.
- 20 7) The solid composition according to any one of claims 1 to 6 wherein the amount of Irbesartan is comprised between 150mg and 300mg of the total weight of the tablet, preferably 300mg or 150mg.
- 8) The solid composition according to any one of claims 1 to 7 wherein the amount of amlodipine besilate is comprised between 5mg and 10mg of the total weight of the tablet, preferably 7mg or 14mg.
- 25 9) The solid composition according to any one of claims 1 to 8 under the form of a tablet wherein the total weight of the tablet is between 400mg and 600mg, preferably 500mg.
- 10) The composition according to any one of claims 1 to 9 having less than 1.50%(w/w) of total impurities for Amlodipine and less than 0.50%(w/w) of total impurities for Irbesartan after 6 months at 40°C/75%RH.
- 30 11) A process for the preparation of a stable oral pharmaceutical composition in a form of a monolayer tablet comprising irbesartan and amlodipine besilate, wherein the process comprises the steps of:

- i. granulating irbesartan and one or more pharmaceutically acceptable excipients, with aqueous solution containing a binder, to form granules,
 - ii. drying the granules;
 - 5 iii. separately blending amlodipine besilate with pharmaceutically acceptable excipients,
 - iv. mixing the irbesartan granules of step ii with the amlodipine besilate blend of step iii);
 - v. lubricating the blend of step iv); optionally after a pre-lubricating step; and
 - vi. compressing the mixture into tablets.
- 10 12) The process of claim 11 wherein the group of pharmaceutically acceptable excipients used in step I and iii) of the process is free of lactose.
- 13) The process according to any one of claims 11 to 12 wherein the pre-lubricating step comprise the mixing of the blend of step (iv) during 10 to 25mn, preferably 20mn before doing the lubricating step.
- 15 14) Use of Irbesartan and amlodipine besilate in the manufacture of a medicament for the treatment of hypertension wherein said medicament is in the stable solid fixed dose composition according to anyone of claim 1 to 10.
- 15) Use according to claim 14 as second line treatment for hypertensive patients not sufficiently controlled using amlodipine as Calcium Channel Blockers (CCB)
- 20 monotherapy or irbesartan as angiotensin II receptor antagonist (ARB).

CLAIMS

- 5 | 1) A stable solid oral pharmaceutical fixed dose composition in a form of a monolayer tablet comprising irbesartan, amlodipine besilate and pharmaceutically acceptable excipients, wherein irbesartan is physically separated from amlodipine besilate and wherein irbesartan under the form of coated granules is embedded in an extragranular matrix comprising amlodipine besilate.
- 10 | ~~1) The composition according to claim 1 wherein irbesartan under the form of coated granules is embedded in an extragranular matrix comprising amlodipine besilate.~~
- 3) ~~2) The composition according to any one of claims 1 to 2, wherein the solid composition takes the form of a monolayer tablet is, preferably film coated.~~
- 3) ~~The composition according to any one of claims 1 to 3 wherein the tablet is further package in suitable packing material such as PVC, PVC / PVdC, PVC / PE / PVdC.~~
- 15 | ~~5) 3) The composition according to any one of claims 1 to 4 2 wherein the irbesartan represents between about 20% and about 70% by weight of the total composition.~~
- ~~6) 4) The composition according to any one of claims 1 to 5 3 wherein the amlodipine besilate represents between about 1% and about 20% by weight of the total composition.~~
- 20 | ~~7) 5) The composition according to any one of claims 1 to 6 4 wherein the pharmaceutically acceptable excipients are selected from the group consisting of diluent, disintegrant, antiadherent, binder lubricant and mixture thereof.~~
- ~~8) 6) The composition according to any one of claims 1 to 7 5 wherein said solid composition is free of lactose.~~
- 25 | ~~9) 7) The solid composition according to any one of claims 1 to 8 6 wherein the amount of Irbesartan is comprised between 150mg and 300mg of the total weight of the tablet, preferably 300mg or 150mg.~~
- ~~10) 8) The solid composition according to any one of claims 1 to 9 7 wherein the amount of amlodipine besilate is comprised between 5mg and 10mg of the total weight of the tablet, preferably 7mg or 14mg.~~
- 30 | ~~11) 9) The solid composition according to any one of claims 1 to 10 8 under the form of a tablet wherein the total weight of the tablet is between 400mg and 600mg, preferably 500mg.~~
-

~~12~~10) The composition according to any one of claims 1 to ~~11~~9 having less than 1.50%(w/w) of total impurities for Amlodipine and less than 0.50%(w/w) of total impurities for Irbesartan after 6 months at 40°C/75%RH.

5 ~~13~~11) A process for the preparation of a stable oral pharmaceutical composition in a form of a monolayer tablet comprising irbesartan and amlodipine besilate, wherein the process comprises the steps of:

- i. granulating irbesartan and one or more pharmaceutically acceptable excipients, with aqueous solution containing a binder, to form granules,
- ii. drying the granules;
- 10 iii. separately blending amlodipine besilate with pharmaceutically acceptable excipients,
- iv. mixing the irbesartan granules of step ii with the amlodipine besilate blend of step iii);
- v. lubricating the blend of step iv); optionally after a pre-lubricating step; and
- 15 vi. compressing the mixture into tablets.

~~14~~12) The process of claim ~~13~~11 wherein the group of pharmaceutically acceptable excipients used in step I and iii) of the process is free of lactose.

20 ~~14~~)The process according to any one of claims 13 or 14 further comprising the step of coating the tablet and packaging in suitable packing material such as PVC, PVC / PVdC, PVC / PE / PVdC.

~~16~~13) The process according to any one of claims ~~13~~11 to ~~15~~12 wherein the pre-lubricating step comprise the mixing of the blend of step (iv) during 10 to 25mn, preferably 20mn before doing the lubricating step.

25 ~~17~~14) Use of Irbesartan and amlodipine besilate in the manufacture of a medicament for the treatment of hypertension wherein said medicament is in the stable solid fixed dose composition according to anyone of claim 1 to ~~12~~10.

~~18~~15) Use according to claim ~~17~~14 as second line treatment for hypertensive patients not sufficiently controlled using amlodipine as Calcium Channel Blockers (CCB) monotherapy or irbesartan as angiotensin II receptor antagonist (ARB).

WO2005/070762 from Sepracor discloses oral formulation under capsules comprising the combination of S-amlodipine and Irbesartan obtained by simple mixing about 25wt% of the two active principles together in the presence of corn starch and about 65wt% of lactose. No problem of stability is raised.

5 WO2008/044862 discloses a combined multi-layered tablet containing amlodipine maleate delayed-immediate-release granules and irbesartan immediate-release layer granules for enabling the two drugs to be chronotherapeutically released, thereby improving the therapeutic activity while reducing side effects. However, such combination is not stable and a high impurity D level appears over the time.

10 Thus, there is no known stable solid dosage form comprising the specific combination of Irbesartan and Amlodipine besilate.

In addition to stability, when formulating solid fixed dose combination, the objective is to provide a patient-convenient combination dosage form of active ingredients that is bioequivalent to the corresponding free-combination of the same active ingredients.

15 As used herein, "fixed-dose-combination or FDC" refers to a combination of two drugs or active ingredients presented in a single dosage unit such as a tablet or oral dosage form.

Further as used herein, "free- combination" refers to a combination of two drugs or active ingredients dosed simultaneously but as two dosage units.

20 As a result of these complex biopharmaceutical properties, development of a fixed-combination dosage form of irbesartan and amlodipine besilate that is bioequivalent to a free-combination thereof is challenging.

Accordingly, a fixed-combination solid dosage formulation of Irbesartan and amlodipine besilate that is stable and bioequivalent to the corresponding free-combination would be desirable.

25 One other challenge faced is homogeneity of Amlodipine in a lubricated blend as the content of Amlodipine in the total tablet weight should be very low compared to the high amount of irbesartan .

30 The object of the present invention is to alleviate at least partly the above mentioned drawbacks.

SUMMARY OF THE INVENTION

35 This object is achieved with a stable solid oral pharmaceutical fixed dose composition comprising irbesartan, amlodipine besilate and pharmaceutically acceptable excipients, wherein irbesartan is physically separated from amlodipine besilate.

This solid dosage form is particularly advantageous since amlodipine besilate does not undergo degradation and this combination product shows reduced and controlled impurities even lesser than with regards to individual reference products of same dose when subjected to stress studies and in finished pack.

WO2005/070762 from Sepracor discloses oral formulation under capsules comprising the combination of S-amlodipine and Irbesartan obtained by simple mixing about 25wt% of the two active principles together in the presence of corn starch and about 65wt% of lactose. No problem of stability is raised.

5 WO2008/044862 discloses a combined multi-layered tablet containing amlodipine maleate delayed-immediate-release granules and irbesartan immediate-release layer granules for enabling the two drugs to be chronotherapeutically released, thereby improving the therapeutic activity while reducing side effects. However, such combination is not stable and a high impurity D level appears over the time.

10 Thus, there is no known stable solid dosage form comprising the specific combination of Irbesartan and Amlodipine besilate.

15 In addition to stability, when formulating solid fixed dose combination, the objective is to provide a patient-convenient combination dosage form of active ingredients that is bioequivalent to the corresponding free-combination of the same active ingredients.

As used herein, "fixed-dose-combination or FDC" refers to a combination of two drugs or active ingredients presented in a single dosage unit such as a tablet or oral dosage form.

20 Further as used herein, "free- combination" refers to a combination of two drugs or active ingredients dosed simultaneously but as two dosage units.

As a result of these complex biopharmaceutical properties, development of a fixed-combination dosage form of irbesartan and amlodipine besilate that is bioequivalent to a free-combination thereof is challenging.

25 Accordingly, a fixed-combination solid dosage formulation of Irbesartan and amlodipine besilate that is stable and bioequivalent to the corresponding free-combination would be desirable.

One other challenge faced is homogeneity of Amlodipine in a lubricated blend as the content of Amlodipine in the total tablet weight should be very low compared to the high amount of irbesartan .

30 The object of the present invention is to alleviate at least partly the above mentioned drawbacks.

SUMMARY OF THE INVENTION

35 This object is achieved with a stable solid oral pharmaceutical fixed dose composition comprising irbesartan, amlodipine besilate and pharmaceutically acceptable excipients, wherein irbesartan is physically separated from amlodipine besilate.

This solid dosage form is particularly advantageous since amlodipine besilate does not undergo degradation and this combination product shows reduced and controlled impurities even lesser than with regards to individual reference products of same dose when subjected to stress studies and in finished pack.



EPO - Munich
18
29. Juni 2012

PATENT DEPARTMENT

☎ direct : + 33 1 55 71 45 67
☎ direct: + 33 1 53 77 94 14
@ : fr.patent@sanofi.com

OFFICE EUROPEEN DES BREVETS
DIRECTION GENERALE 2
Erhardtstrasse, 27
D-80469 MUNICH
ALLEMAGNE

By mail

Paris, June 21, 2012

Your Ref :
Our Ref : FR2009/028-EP/EPT
BCT/KPE-12-04513

Object : Application No: 09744185.1 – 1219 – PCT/IB2009007027

Dear Sirs,

We refer to your letter dated of February 9, 2012 being a communication pursuant to Rules 161(1) and 162 EPC which has a due date for response of August 20, 2012.

In responding to this Official Action, the Applicant would wish to submit herewith a revised set of claims 1-15 and an amendment of the page 3 of the previous description. In addition, we enclosed a copy of the original set of claims and the original page 3 of the description with our proposed amendments marked.

Any amendment should not be construed as an abandon of subject matter. The Applicant reserves the right to file Divisional applications to subject matter which has been deleted from the claims or which is no longer covered by the scope of the amended claims.

No matter has been added so it is believed that these amendments do not contravene Article 123(2).

Taking the relevant points in order from the Written Opinion of the International Searching Authority (ISA):

1- Item V

I. The reference to documents D1 has been noted.

2. Novelty

The International Written Opinion alleges that the subject matter of claims 1, 4-7, 9, 10, 12, 17 and 18 lack of novelty in view of the document D1.

Without acquiescing to the Examiner's assertion and merely as a means to advance the prosecution of the present case, we have amended the objected claims to be clearly delimited against the disclosure of D1.

Accordingly, in the revised claims submitted the previously presented claims 1 to 18 have been amended as follows:

- Original Claim 1 has been redrafted in order to amend so that the new claim 1 is a combination of the old claims 1, 2 and 3;
- New claim 2 corresponds to previous claim 3 and has been amended by deleting the subject matter incorporated in claim 1;
- The original claims 2, 4 and 15 have been deleted;
- The term "about" used in the original claims 5 and 6 has been deleted;
- New claim 11 corresponds to previous claim 13 and has been amended by specifying that the composition is in the form of a monolayer tablet. Support for this amendments can be found throughout the description, e.g., at page 6 lines 23-24.
- Original claims 3 to 18 have been also amended with respect to theirs numbering and dependencies (new claims 2 to 15).

The presently claimed invention now relates to a stable solid oral pharmaceutical fixed dose composition in a form of a monolayer tablet comprising irbesartan, amlodipine besilate and pharmaceutically acceptable excipients, wherein irbesartan is physically separated from amlodipine besilate and wherein irbesartan under the form of coated granules is embedded in an extragranular matrix comprising amlodipine besilate.

D1 discloses a combined multi-layered tablet containing amlodipine maleate delayed-immediate-release granules as a first layer and irbesartan immediate-release layer granules as a second layer. D1 also relates to a preparation of multi-layered tablets consisting to separately prepare delayed-immediate-release granules of amlodipine and immediate-release granules of irbesartan; separately introduce each type of granules into different inlet of a multi-layered tablet press for compression and then coated the multi-layered tablet.

However, D1 does not disclose a stable fixed dose composition in a form of a monolayer tablet comprising irbesartan and amlodipine besilate wherein irbesartan is physically separated from amlodipine besilate and wherein irbesartan under the form of coated granules is embedded in an extragranular matrix comprising amlodipine besilate. D1 does also not disclose a process for the preparation of a stable oral pharmaceutical composition in a form of a monolayer tablet comprising irbesartan and amlodipine besilate, wherein the process comprises the steps of granulating irbesartan to form granules, separately blending amlodipine besilate with excipients, then mixing the irbesartan granules with the amlodipine besilate blend and then compressing the mixture into a monolayer tablet.

In view of the above-provided analysis the Examiner is respectfully requested to reconsider his objections of novelty for previous claims 2, 3, 8, 11, 13-16 and acknowledge novelty for the subject matter of the amended claims 1-15.

3. Inventive Step

The Examiner has further raised objections with respect to inventiveness of the subject matter of previous claims 1-18. Allegedly, the problem underlying the present invention resides in the provision of an alternative process for the preparation of an oral pharmaceutical composition comprising irbesartan and amlodipine besylate. Considering the subject matter of the claims 1-18 the solution to this problem, the Examiner has denied inventive step as a surprising technical effect is allegedly missing.

We respectfully disagree with the assessment.

The gist of the present invention resides in the provision of pharmaceutical monolayer tablets comprising irbesartan and amlodipine besilate, wherein the amlodipine besilate does not undergo degradation and the tablet has reduced level of total impurities on long term stability and wherein the combination product has a dissolution profile equivalent to the corresponding free immediate release combination of the same active compounds.

The closest prior art is considered to be D1.

The feature distinguishing the claimed invention from the prior art resides in the presence of a tablet of irbesartan and amlodipine besilate (not amlodipine maleate), wherein only irbesartan is in the intragranular material, the irbesartan granules being embedded in an extragranular matrix comprising amlodipine besilate, wherein the tablet is a monolayer tablet and both irbesartan and amlodipine are released immediately.

This feature renders the claimed composition advantageous as it shows reduced and controlled impurities when subjected to stress stability studies.

Thus, the problem underlying the present invention can be formulated to reside in the provision of a fixed dose composition comprising irbesartan and amlodipine besilate which does not undergo degradation of the active compounds over the time.

The solution to this problem is the claimed composition.

This solution is not obvious over D1, as D1 does not comment on this stability issue and reduced level of impurities. On its face, reference D1 does not provide the skilled person with any guidance how to achieve this, let alone provides any motivation to modify the bi-layered tablet of immediate-release irbesartan and delayed-immediate-release amlodipine maleate such as to arrive at the subject matter of the instant claims. In view of the number of possibilities to modify the compositions of D1, the skilled person would not necessary have considered the claimed compositions.

Consequently, it is respectfully submitted that the invention as amended meets the requirements in the assessment of the inventive step over D1.

54

2- Item VII

The International Written Opinion indicates that the relevant background art in D1 is not mentioned in the description.

Accordingly, in the revised submitted page 3 of the description, the prior art D1 is now mentioned.

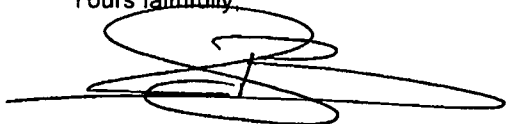
3- Item VIII

We would hope that the amendments to the claims submitted herewith address the Examiners' objections (deletion of the previous claims 4 and 15, deletion of the term "about" in the previous claims 5 and 6).

Concerning the previous claim 12, the Examiner has stated that the claims lack clarity because the claim attempts to define the subject-matter in term of a result to be achieved. Applicant respectfully disagrees. Applicant's invention resides in recognizing that a stable amlodipine besilate – irbesartan monolayer composition can be formulated using irbesartan under the form of coated granules and an extragranular matrix comprising amlodipine besilate which embedded the irbesartan granules. Applicant has provided the benefit of this discovery to the art via the instant application to claim the full breadth of the invention.

It is respectfully requested that the examination procedure in this application be conducted on the basis of the amended set of claims submitted herewith and that, in view of the amendments made to the claims and the above submitted facts and arguments, the Examiner reconsider the objections raised in the international phase and acknowledge patentability for the amended set of claims.

Yours faithfully,



CARION TARAVELLA Brigitte