(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 January 2012 (05.01.2012)

PCT

(10) International Publication Number
WO 2012/001641 A1

(51) **International Patent Classification:**
A61K 45/06 (2006.01) ***A61K 38/00*** (2006.01)
A61K 31/70 (2006.01) ***A61K 47/06*** (2006.01)

(21) **International Application Number:**
PCT/IB20 11/052864

(22) **International Filing Date:**
29 June 201 1 (29.06.201 1)

(25) **Filing Language:** English

(26) **Publication Language:** English

(30) **Priority Data:**
PCT/IB20 10/052983 30 June 2010 (30.06.2010) IB

(71) **Applicant** *(for all designated States except US):* **ACTELION PHARMACEUTICALS LTD** [CH/CH]; Gewerbestrasse 16, CH-4123 Allschwil (CH).

(72) **Inventors; and**

(75) **Inventors/ Applicants** *(for US only):* **ABIAN, Olga** [ES/ES]; Universidad de Zaragoza, c/o Departamento de Bioquimica, Facultad de Ciencias, E-50009 Zaragoza (ES). **ALFONSO, Pilar** [ES/ES]; Universidad de Zaragoza, c/o Departamento de Bioquimica, Facultad de Ciencias, E-50009 Zaragoza (ES). **GIRALDO, Pilar** [ES/ES]; Universidad de Zaragoza, c/o Departamento de Bioquimica, Facultad de Ciencias, E-50009 Zaragoza (ES). **POCOVI, Miguel** [ES/ES]; Universidad de Zaragoza, c/o Departamento de Bioquimica, Facultad de Ciencias, E-50009 Zaragoza (ES). **SANCHO, Javier** [ES/ES]; Universidad de Zaragoza, c/o Departamento de Bioquimica, Facultad de Ciencias, E-50009 Zaragoza (ES).

(74) **Agent: RUHLMANN, Eric;** c/o Actelion Pharmaceuticals Ltd, Legal Department, Gewerbestrasse 16, CH-4123 Allschwil (CH).

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available):* AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available):* ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2012/001641 A1

(54) **Title:** STABLE PHARMACEUTICAL COMPOSITIONS

(57) **Abstract:** The invention relates to stable pharmaceutical compositions comprising a human β-glucocerebrosidase or an analogue thereof and miglustat.

STABLE PHARMACEUTICAL COMPOSITIONS

The present invention relates to stable pharmaceutical compositions comprising a human β-glucocerebrosidase or an analogue thereof and miglustat.

Human β-glucocerebrosidase and/or synthetic analogues thereof, such as imiglucerase (commercially available under the trademark Cerezyme®) or velaglucerase alfa (commercially available under the trademark Vpriv®), are enzymes used in the Enzyme Replacement Therapy (hereafter ERT) treatment of Gaucher disease.

A major drawback of the ERT enzymes is their relatively low stability. Thus pharmaceutical products containing such enzymes are provided as freeze-dried formulations that must be stored in a refrigerator. Similarly, the liquid formulations obtained after reconstitution with water are to be used right away as the ERT enzyme is unstable.

An alternative treatment to the ERT treatment of Gaucher disease is a substrate replacement therapy using the iminosugar miglustat *(N*-butyl-deoxynojirimycin), commercially available under the trademark Zavesca®.

WO 00/62779 discloses the synergistic effect of the combined use of an inhibitor of glycolipid synthesis (such as miglustat) and an agent capable of increasing the rate of glycolipid degradation (such as human β-glucocerebrosidase or an analogue thereof) for simultaneous, sequential or separate use in the treatment of, among others, Gaucher disease. Data about the use of the combination of miglustat and β-glucocerebrosidase are reported in WO 00/62779 as well as in an article by Priestman et al. *{Glycobiology* (2000), **10**(**l** l), iv-ix).

No concrete pharmaceutical composition comprising miglustat and an ERT enzyme together is however described in these documents. A reason for the absence of pharmaceutical compositions comprising both miglustat and an ERT enzyme is that miglustat can be administered orally whereas the ERT enzyme has to be administered by infusion (because it would be degraded if it went through the gastrointestinal tract). As a result, to offer a combined treatment with an ERT enzyme and miglustat, one skilled in the

art would not combine miglustat and an ERT enzyme in the same formulation; instead, he would provide the two components separately, namely miglustat in the form of capsules for oral administration and the ERT enzyme in the form of a solid composition to be reconstituted with water for intravenous administration.

It has now been surprisingly found that, under certain conditions, miglustat has the ability to stabilise solid and liquid pharmaceutical compositions comprising human β-glucocerebrosidase or a synthetic analogue thereof. The quantity of miglustat required to obtain this stabilising effect can be much lower than the dose that would be used to obtain a therapeutic effect of miglustat itself.

Various embodiments of the invention are presented hereafter:

1) The invention thus firstly relates to the use of miglustat to stabilise a pharmaceutical composition comprising an enzyme selected from human β-glucocerebrosidase and synthetic analogues of human β-glucocerebrosidase.

The following paragraphs provide definitions of various terms used herein and are intended to apply uniformly throughout the specification and claims, unless an otherwise expressly set out definition provides a broader or narrower definition:

- A "synthetic analogue of human β-glucocerebrosidase" refers to an analogue of human β-glucocerebrosidase either obtained by recombinant technology or to a modified form of human β-glucocerebrosidase where the non-reducing ends of the oligosaccharide chains have been terminated with mannose residues. Representative examples of synthetic analogues of human β-glucocerebrosidase include imiglucerase, velaglucerase alfa, taliglucerase alfa and alglucerase. Preferred are imiglucerase and velaglucerase alfa.

- A "normal saline solution" refers to a sodium chloride solution obtained by dissolving about 9 grams of sodium chloride (NaCl) in 1 liter of distilled water.

- A "half-normal saline solution" refers to a sodium chloride solution obtained by dissolving about 4.5 grams of sodium chloride (NaCl) and about 4.5 grams glucose in 1 liter of distilled water.

- A "lactated Ringer's solution" refers to a water solution containing about 130 mmol/L sodium ions, about 109 mmol/L chloride ions, about 28 mmol/L lactate ions, about 4 mmol/L potassium ions and about 1.5 mmol/L calcium ions.

- Unless used regarding temperatures or pH values, the term "about" placed before a numerical value "X" refers in the current application to an interval extending from X minus 10% of X to X plus 10% of X, and preferably to an interval extending from X minus 5% of X to X plus 5% of X. In the particular case of temperatures, the term "about" placed before a temperature "Y" refers in the current application to an interval extending from the temperature Y minus 10°C to Y plus 10°C, and preferably to an interval extending from Y minus 5°C to Y plus 5°C. Furthermore, in the case of pH values, the term "about" placed before a pH value "Z" refers in the current application to an interval extending from the pH Z minus 0.2 pH unit to Z plus 0.2 pH unit, and preferably to an interval extending from Z minus 0.1 pH unit to Z plus 0.1 pH unit.

2) According to a sub-embodiment of embodiment 1), the enzyme will be imiglucerase.

3) According to another sub-embodiment of embodiment 1), the enzyme will be velaglucerase alfa.

4) According to a further sub-embodiment of embodiment 1), the enzyme will be taliglucerase alfa.

5) According to yet a further sub-embodiment of embodiment 1), the enzyme will be alglucerase.

6) According to one main variant of this invention, the use according to embodiments 1) to 5) will be to stabilise a liquid composition.

7) According to the other main variant of this invention, the use according to embodiments 1) to 5) will be to stabilise a solid composition.

8) Preferably, for the use according to embodiments 1) to 7), the molar ratio of miglustat used with respect to the enzyme will be from 25 to 75 moles of miglustat per mole of enzyme, notably from 40 to 60 moles of miglustat per mole of enzyme, and in particular about 50 moles of miglustat per mole of enzyme.

9) The invention also relates to a liquid pharmaceutical composition, comprising:

a) an enzyme selected from human β-glucocerebrosidase and synthetic analogues thereof and

b) miglustat,

wherein the pH of said liquid pharmaceutical composition is a pH of from 6 to 8.

10) Preferably, the pH of the liquid pharmaceutical composition according to embodiment 9) will be from 6.5 to 7.5 (and in particular from 6.7 to 7.5 and notably about 7.2).

11) According to more specific sub-embodiments of embodiments 9) or 10), the liquid pharmaceutical composition according to embodiment 9) or 10) will be any water solution suitable for injection to which the enzyme and miglustat have been added, said liquid pharmaceutical composition being in particular selected from a normal saline solution, a half-normal saline solution and a lactated Ringer's solution, to which the enzyme and miglustat have been added.

12) In particular, the liquid pharmaceutical composition according to embodiment 11) will be a normal saline solution to which the enzyme and miglustat have been added.

13) According to particular sub-embodiments of embodiments 9) to 12), the enzyme will be imiglucerase.

14) According to other particular sub-embodiments of embodiments 9) to 12), the enzyme will be velaglucerase alfa.

15) According to further particular sub-embodiments of embodiments 9) to 12), the enzyme will be taliglucerase alfa.

16) According to yet further particular sub-embodiments of embodiments 9) to 12), the enzyme will be alglucerase.

17) Preferably, the molar ratio of miglustat with respect to the enzyme in the liquid composition according to one of embodiments 9) to 16) will be from 25 to 75 moles of

miglustat per mole of enzyme, notably from 40 to 60 moles of miglustat per mole of enzyme, and in particular about 50 moles of miglustat per mole of enzyme.

18) The invention furthermore relates to a solid pharmaceutical composition, comprising:

a) an enzyme selected from human β-glucocerebrosidase and synthetic analogues thereof and

b) miglustat,

wherein the pH of the solution obtained after adding water to said solid pharmaceutical composition is a pH of from 6 to 8.

19) Preferably, the pH of the solution obtained after adding water to the solid pharmaceutical composition according to embodiment 18) will be from 6.5 to 7.5 (and in particular from 6.8 to 7.2).

20) According to a sub-embodiment of embodiment 18) or 19), the enzyme will be imiglucerase.

21) According to another sub-embodiment of embodiment 18) or 19), the enzyme will be velaglucerase alfa.

22) According to a further sub-embodiment of embodiment 18) or 19), the enzyme will be taliglucerase alfa.

23) According to yet a further sub-embodiment of embodiment 18) or 19), the enzyme will be alglucerase.

24) Preferably, the molar ratio of miglustat with respect to the enzyme in the solid composition according to one of embodiments 18) to 23) will be from 25 to 75 moles of miglustat per mole of enzyme, notably from 40 to 60 moles of miglustat per mole of enzyme, and in particular about 50 moles of miglustat per mole of enzyme.

25) The invention also relates to a pharmaceutical composition according to one of embodiments 9) to 24) for use in the treatment of Gaucher disease (notably for use in the treatment of Gaucher disease type 1).

26) The invention furthermore relates to a method of treating a patient having Gaucher disease (notably Gaucher disease type 1), said method comprising administering by intravenous route to said patient an effective amount of a liquid pharmaceutical composition according to one of embodiments 9) to 17).

27) The invention moreover relates to a method of treating a patient having Gaucher disease (notably Gaucher disease type 1), said method comprising administering by intravenous route to said patient a solution obtained by adding water to a solid pharmaceutical composition according to one of embodiments 18) to 24).

The production of the pharmaceutical compositions according to this invention can be effected in a manner which will be familiar to any person skilled in the art (see for example Remington, *The Science and Practice of Pharmacy*, 21st Edition (2005), Part 5, "Pharmaceutical Manufacturing" [published by Lippincott Williams & Wilkins]) by bringing the described components, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

The solid pharmaceutical solutions according to this invention can in particular be obtained by lyophilising water solutions containing the respective components in the appropriate proportions.

Particular embodiments of the invention are described in the following Examples, which serve to illustrate the invention in more detail without limiting its scope in any way.

EXAMPLES

Example 1: liquid composition containing imiglucerase and miglustat:

A water solution was prepared (using distilled water) which contains the components listed in the table hereafter:

Component	Concentration
Sodium chloride	164 mM
Sodium phosphate	10 mM
Imiglucerase	4 μM
Miglustat	200 μM

The pH measured for this water solution is 7.2.

Example 2: solid composition containing imiglucerase and miglustat:

The water solution of Example 1 may be freeze-dried to give a solid composition.

Example 3: liquid composition containing velaglucerase alfa and miglustat:

A water solution was prepared (using distilled water) which contains the components listed in the table hereafter:

Sodium chloride	164 mM
Sodium phosphate	10 mM
Velaglucerase alfa	4 μM
Miglustat	200 μM

The pH measured for this water solution is 7.2.

Example 4: solid composition containing velaglucerase alfa and miglustat:

The water solution of Example 4 may be freeze-dried to give a solid composition.

Experimental results

The stability of the compositions of Examples 1 and 3, in comparison with reference compositions which contain the same enzyme but not miglustat or have a slightly acidic pH, has been studied thanks to the methods described hereafter.

Reference compositions:

Reference liquid composition RE1:

A water solution was prepared (using distilled water) which contains the components listed in the table hereafter:

Component	Concentration
Sodium chloride	164 mM
Sodium phosphate	10 mM
Imiglucerase	4 μM

The pH measured for this reference liquid composition was 7.2.

Reference liquid composition RE2:

A water solution was prepared (using distilled water) which contains the components listed in the table hereafter:

Component	Concentration
Sodium chloride	178 mM
Sodium acetate	10 mM
Imiglucerase	4 μM

The pH measured for this reference liquid composition was 5.

Reference liquid composition RE3:

A water solution was prepared (using distilled water) which contains the components listed in the table hereafter:

Component	Concentration
Sodium chloride	178 mM
Sodium acetate	10 mM
Imiglucerase	4 μM
Miglustat	200 μM

The pH measured for this reference liquid composition was 5.

Reference liquid composition RE4:

A water solution was prepared (using distilled water) which contains the components listed in the table hereafter:

Component	Concentration
Sodium chloride	164 mM
Sodium phosphate	10 mM
Velaglucerase alfa	4 μM

The pH measured for this reference liquid composition was 7.2.

Reference liquid composition RE5:

A water solution was prepared (using distilled water) which contains the components listed in the table hereafter:

Component	Concentration
Sodium chloride	178 mM
Sodium acetate	10 mM
Velaglucerase alfa	4 μM

The pH measured for this reference liquid composition was 5.

Reference liquid composition RE6:

A water solution was prepared (using distilled water) which contains the components listed in the table hereafter:

Component	Concentration
Sodium chloride	178 mM
Sodium acetate	10 mM
Velaglucerase alfa	4 μM
Miglustat	200 μM

The pH measured for this reference liquid composition was 5.

Differential Scanning Calorimetry test:

The heat capacity of the proteins was measured as a function of temperature with a high precision differential scanning VP-DSC microcalorimeter (MicroCal, Northampton, MA). Protein samples and reference solutions were properly degassed and carefully loaded into the cells to avoid bubble formation. Thermal denaturation scans were performed with freshly prepared buffer-exchanged protein solutions. The baseline of the instrument was routinely recorded before the experiments. Experiments were performed in 164 mM NaCl,

10 mM sodium phosphate, pH 7.2 or 178 mM NaCl, 10 mM sodium acetate, pH 5, at a scanning rate of 1 °C/min. Data were analyzed using software developed in our laboratory implemented in Origin 7 (OriginLab).

In the case of imiglucerase, a thermodynamic model could not be applied to analyze the data because severe aggregation upon denaturation occurred. This phenomenon had been previously reported (Lieberman et al, *Biochemistry* (2009), **48,** 4816-4827). In this case, the analysis was limited to differences in the temperature at maximum heat capacity T_m of the normalized data.

Differential Scanning Calorimetry results:

The temperatures at maximum heat capacity T_m obtained by performing the Differential Scanning Calorimetry test described in the preceding section regarding the compositions containing imiglucerase are summarised in Table 1 hereafter. Those obtained regarding the compositions containing velaglucerase alfa are summarised in Table 2 hereafter.

Composition	T_m
RE1	50.0
Example 1	50.4
RE2	55.3
RE3	55.3

Table 1

Composition	T_m
RE3	50.2
Example 2	50.6
RE4	55.5
RE6	55.5

Table 2

As can be seen from Tables 1 and 2:

- There is no difference in T_m between the reference compositions RE2 and RE3 or between the reference compositions RE5 and RE6. Thus, miglustat does not stabilise imiglucerase or velaglucerase alfa at pH 5.
- There is a difference of 0.4 °C in T_m between the composition of Example 1 and the reference composition REl. This significant T_m difference shows that miglustat stabilises imiglucerase at pH 7.2.
- There is also a difference of 0.4 °C in T_m between the composition of Example 2 and the reference composition RE4. This significant T_m difference shows that miglustat stabilises velaglucerase alfa at pH 7.2.

Claims

1. Use of miglustat to stabilise a pharmaceutical composition comprising an enzyme selected from human β-glucocerebrosidase and synthetic analogues thereof.

2. Use according to claim 1, wherein the enzyme is imiglucerase.

3. Use according to claim 1, wherein the enzyme is velaglucerase alfa.

4. Use according to claim 1, wherein the enzyme is taliglucerase alfa.

5. Use according to claim 1, wherein the enzyme is alglucerase.

6. A liquid pharmaceutical composition, comprising:

c) an enzyme selected from human β-glucocerebrosidase and synthetic analogues thereof and

d) miglustat,

wherein the pH of said liquid pharmaceutical composition is a pH of from 6 to 8.

7. A liquid pharmaceutical composition according to claim 6, which has a pH of from 6.5 to 7.5.

8. A liquid pharmaceutical composition according to claim 6 or 7, wherein the enzyme is imiglucerase.

9. A liquid pharmaceutical composition according to claim 6 or 7, wherein the enzyme is velaglucerase alfa.

10. A liquid pharmaceutical composition according to claim 6 or 7, wherein the enzyme is taliglucerase alfa.

11. A liquid pharmaceutical composition according to claim 6 or 7, wherein the enzyme is alglucerase.

12. A solid pharmaceutical composition, comprising:

a) an enzyme selected from human β-glucocerebrosidase and synthetic analogues thereof and

b) miglustat,

wherein the pH of the solution obtained after adding water to said solid pharmaceutical composition is a pH of from 6 to 8.

13. A solid pharmaceutical composition according to claim 12, wherein the pH of the solution obtained after adding water to said solid pharmaceutical composition is a pH of from 6.5 to 7.5.

14. A solid pharmaceutical composition according to claim 12 or 13, wherein the enzyme is imiglucerase.

15. A solid pharmaceutical composition according to claim 12 or 13, wherein the enzyme is velaglucerase alfa.

16. A solid pharmaceutical composition according to claim 12 or 13, wherein the enzyme is taliglucerase alfa.

17. A solid pharmaceutical composition according to claim 12 or 13, wherein the enzyme is alglucerase.

18. A pharmaceutical composition according to one of claims 6 to 17 for use in the treatment of Gaucher disease.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2011/052864

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K45/06 A61K31/70 A61K38/00 A61K47/06
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal , BIOSIS, CHEM ABS Data, EMBASE, FSTA, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/07078 A1 (SEARLE & CO [US]; JACOB GARY S [US]; DWEK RAYMOND A [GB]) 1 February 2001 (2001-02-01)	1,5-7, 11-13, 17, 18
Y	page 1, paragraph 1 - page 2, last paragraph page 8, paragraphs 3,4 claims 1-13; examples 1-2 table 1	1-18

X	US 2006/204487 A1 (SHAALTIEL YOSEPH [IL] ET AL) 14 September 2006 (2006-09-14)	1,4,6,7, 10, 12, 13, 16, 18
Y	figures 5a-d paragraphs [0002], [0044], [0058], [0060], [0061], [0076], [0088], [0097] paragraphs [0186], [0226], [0228]	1-18

	-/--	

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 October 2011	08/11/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Hbrtner, Michael

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2011/052864

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 321 143 Al (OXFORD GLYCOSCIENCES UK LTD [GB]) 25 June 2003 (2003-06-25)	1,5-7, 11-13, 17, 18
Y	paragraphs [0001] - [0015] paragraphs [0020] - [0034] claims 1-10	1-18

X	W0 2004/037373 A2 (SCRIPPS RESEARCH INST [US]; KELLY JEFFREY W [US]; SAWKAR ANU R [US]; B) 6 May 2004 (2004-05-06)	1-18
Y	page 4, lines 4-10 page 5, line 12 - page 6, line 17 page 7, lines 26-33 page 8, line 21 - page 10, line 21 page 23, paragraph 1 figure 4 claims 1-17	1-18

X	ZIMRAN ARI ET AL: "Gaucher disease and the clinical experience with substrate reduction therapy. ", PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY OF LONDON B BIOLOGICAL SCIENCES, vol. 358, no. 1433, 29 May 2003 (2003-05-29), pages 961-966, XP009153443, ISSN: 0962-8436	1,2,6-8, 12-14
Y	abstract page 963, right-hand column, last paragraph - page 965, left-hand column, paragraph 2	1-18

Y	ALFONSO ET AL: "Miglustat (NB-DNJ) works as a chaperone for mutated acid beta-glucosidase in cells transfected with several Gaucher disease mutations", BLOOD CELLS, MOLECULES AND DISEASES, LAJ0LLA, US, vol. 35, no. 2, 1 September 2005 (2005-09-01), pages 268-276, XP005074539, ISSN: 1079-9796, D0I: 10.1016/J.BCMD.2005.05.007 abstract	1-18

Y	WEINREB NEAL J ET AL: "Guidance on the use of miglustat for treating patients with type 1 Gaucher disease", AMERICAN JOURNAL OF HEMATOLOGY, vol. 80, no. 3, November 2005 (2005-11), pages 223-229, XP009153444, ISSN: 0361-8609 abstract page 228, "Recommendations", point 6	1-18

-/--

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2011/052864

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JOSE L. CAPABLO ET AL: "Neurologic Improvement in a Type 3 Gaucher Disease Patient Treated with Imiglucerase/Miglustat Combination", EPILEPSIA, vol. 48, no. 7, 1 July 2007 (2007-07-01), pages 1406-1408, XP55010307, ISSN: 0013-9580, DOI: 10.1111/j.1528-1167.2007.01074.x abstract --- A. ZIMRAN ET AL: "Phase 1/2 and extension study of velaglucerase alfa replacement therapy in adults with type 1 Gaucher disease: 48-month experience", BLOOD, vol. 115, no. 23, 18 March 2010 (2010-03-18), pages 4651-4656, XP55010530, ISSN: 0006-4971, DOI: 10.1182/blood-2010-02-268649 abstract Discussion ---	1-18
Y		1-18
L	Anonymous: "Cerezyme/imiglucerase product data sheet", , 25 October 2011 (2011-10-25), XP55010420, Retrieved from the Internet: URL: http://www.cerezyme.com/"/media/Files/CerezymeUS/pdf/cerezyme_pi.pdf [retrieved on 2011-10-25] the whole document ---	
A	SANCHEZ-0LLE G ET AL: "Promising results of the chaperone effect caused by iminosugars and aminocyclitol derivatives on mutant glucocerebrosidases causing Gaucher disease", BLOOD CELLS, MOLECULES AND DISEASES, LAJ0LLA, US, vol. 42, no. 2, 1 March 2009 (2009-03-01), pages 159-166, XP025915574, ISSN: 1079-9796, DOI: 10.1016/J.BCMD.2008.11.002 [retrieved on 2009-01-22] the whole document ---	1-18

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2011/052864

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0107078 A1	01-02-2001	AT 234626 T	15-04-2003
		AU 6050600 A	13-02-2001
		CA 2378776 A1	01-02-2001
		DE 60001745 D1	24-04-2003
		DE 60001745 T2	04-03-2004
		EP 1196190 A1	17-04-2002
		JP 2003505430 A	12-02-2003
US 2006204487 A1	14-09-2006	AU 2004234635 A1	11-11-2004
		BR PI0410520 A	20-06-2006
		CA 2523539 A1	11-11-2004
		CN 1875111 A	06-12-2006
		EP 1618177 A2	25-01-2006
		EP 2322636 A1	18-05-2011
		EP 2343378 A1	13-07-2011
		EP 2330204 A1	08-06-2011
		EP 2330205 A1	08-06-2011
		EP 2333083 A1	15-06-2011
		WO 2004096978 A2	11-11-2004
		JP 2006524506 A	02-11-2006
		JP 2011184445 A	22-09-2011
		KR 20060018826 A	02-03-2006
		MX PA05011507 A	03-07-2006
		RU 2009148012 A	27-06-2011
		ZA 200508680 A	29-10-2008
EP 1321143 A1	25-06-2003	NONE	
W0 2004037373 A2	06-05-2004	AU 2003284886 A1	13-05-2004