



US008846695B2

(12) **United States Patent**
Dugi

(10) **Patent No.:** **US 8,846,695 B2**
(45) **Date of Patent:** **Sep. 30, 2014**

(54) **TREATMENT FOR DIABETES IN PATIENTS WITH INADEQUATE GLYCEMIC CONTROL DESPITE METFORMIN THERAPY COMPRISING A DPP-IV INHIBITOR**

(75) Inventor: **Klaus Dugi**, Dresden (DE)

(73) Assignee: **Boehringer Ingelheim International GmbH**, Ingelheim am Rhein (DE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 148 days.

(21) Appl. No.: **13/143,370**

(22) PCT Filed: **Jan. 7, 2010**

(86) PCT No.: **PCT/EP2010/050103**

§ 371 (c)(1),
(2), (4) Date: **Aug. 18, 2011**

(87) PCT Pub. No.: **WO2010/079197**

PCT Pub. Date: **Jul. 15, 2010**

(65) **Prior Publication Data**

US 2011/0301182 A1 Dec. 8, 2011

(30) **Foreign Application Priority Data**

Jan. 7, 2009 (EP) 09150159

(51) **Int. Cl.**
A61K 31/52 (2006.01)

(52) **U.S. Cl.**
USPC **514/263.21**

(58) **Field of Classification Search**
USPC 514/263.21
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

- 2,056,046 A 9/1936 Fourneau
- 2,375,138 A 5/1945 Victors
- 2,629,736 A 2/1953 Krimmel
- 2,730,544 A 1/1956 Sahyun
- 2,750,387 A 6/1956 Krimmel
- 2,928,833 A 3/1960 Leake et al.
- 3,174,901 A 3/1965 Sterne
- 3,236,891 A 2/1966 Seemuller
- 3,454,635 A 7/1969 Muth
- 3,673,241 A 6/1972 Marxer
- 3,925,357 A 12/1975 Okada et al.
- 4,005,208 A 1/1977 Bender et al.
- 4,061,753 A 12/1977 Bodor et al.
- 4,382,091 A 5/1983 Benjamin et al.
- 4,599,338 A 7/1986 Regnier et al.
- 4,639,436 A 1/1987 Junge et al.
- 4,687,777 A 8/1987 Meguro et al.
- 4,743,450 A 5/1988 Harris et al.
- 4,816,455 A 3/1989 Schickaneder et al.
- 4,873,330 A 10/1989 Lindholm
- 4,968,672 A 11/1990 Jacobson et al.

- 5,084,460 A 1/1992 Munson, Jr. et al.
- 5,130,244 A 7/1992 Nishimaki et al.
- 5,219,870 A 6/1993 Kim
- 5,223,499 A 6/1993 Greenlee et al.
- 5,234,897 A 8/1993 Findeisen et al.
- 5,258,380 A 11/1993 Janssens et al.
- 5,266,555 A 11/1993 Findeisen et al.
- 5,273,995 A 12/1993 Roth
- 5,284,967 A 2/1994 Macher
- 5,300,298 A 4/1994 LaNoue
- 5,329,025 A 7/1994 Wong et al.
- 5,332,744 A 7/1994 Chakravarty et al.
- 5,389,642 A 2/1995 Dorsch et al.
- 5,399,578 A 3/1995 Buhlmayer et al.
- 5,407,929 A 4/1995 Takahashi et al.
- 5,470,579 A 11/1995 Bonte et al.
- 5,591,762 A 1/1997 Huel et al.
- 5,594,003 A 1/1997 Huel et al.
- 5,602,127 A 2/1997 Huel et al.
- 5,614,519 A 3/1997 Huel et al.
- 5,719,279 A 2/1998 Kufner-Muhl et al.
- 5,728,849 A 3/1998 Bouchard et al.
- 5,753,635 A 5/1998 Buckman et al.
- 5,830,908 A 11/1998 Grunenberg et al.

(Continued)

FOREIGN PATENT DOCUMENTS

- AU 2003280680 A1 6/2004
- AU 2009224546 A1 9/2009
- CA 1123437 A1 5/1982
- CA 2136288 A1 5/1995
- CA 2418656 A1 2/2002
- CA 2496249 A1 3/2004
- CA 2496325 A1 3/2004
- CA 2498423 A1 4/2004
- CA 2505389 A1 5/2004
- CA 2508233 A1 6/2004

(Continued)

OTHER PUBLICATIONS

- Eckhardt et al., Journal of Med. Chem., 2007, 50:6450-6453.*
- Graefe-Mody et al. publication, Current Medical Research and Opinion, 2009, 25(8): 1963-1972.*
- International Search Report and Written Opinion for PCT/EP2010/050103 mailed Mar. 22, 2010.
- International Search Report and Written Opinion for PCT/EP2011/057163 mailed Jun. 27, 2011.
- International Search Report for PCT/EP2008/060740 mailed Mar. 30, 2009.
- International Search Report for PCT/EP2010/051093 mailed Jul. 14, 2010.

(Continued)

Primary Examiner — Rei-tsang Shiao
(74) *Attorney, Agent, or Firm* — Michael P. Morris; David L. Kershner

(57) **ABSTRACT**

The present invention relates to the finding that certain DPP-4 inhibitors are particularly suitable for improving glycemic control in type 2 diabetes patients with inadequate glycemic control despite metformin therapy.

(56)

References Cited

U.S. PATENT DOCUMENTS

5,879,708	A	3/1999	Makino et al.	2003/0224043	A1	12/2003	Appel et al.
5,958,951	A	9/1999	Ahrndt et al.	2003/0232987	A1	12/2003	Dahanukar et al.
5,965,555	A	10/1999	Gebert et al.	2003/0236272	A1	12/2003	Carr
5,965,592	A	10/1999	Buhlmayer et al.	2004/0023981	A1	2/2004	Ren et al.
6,011,049	A	1/2000	Whitcomb	2004/0034014	A1	2/2004	Kanstrup et al.
6,107,302	A	8/2000	Carter et al.	2004/0063725	A1	4/2004	Barth et al.
6,166,063	A	12/2000	Villhauer	2004/0077645	A1	4/2004	Himmelsbach et al.
6,248,758	B1	6/2001	Klokkers et al.	2004/0082570	A1	4/2004	Yoshikawa et al.
6,303,661	B1	10/2001	Demuth et al.	2004/0087587	A1	5/2004	Himmelsbach et al.
6,342,601	B1	1/2002	Bantick et al.	2004/0097510	A1	5/2004	Himmelsbach et al.
6,372,940	B1	4/2002	Cavazza	2004/0116328	A1	6/2004	Yoshikawa et al.
6,548,481	B1	4/2003	Demuth et al.	2004/0122048	A1	6/2004	Benjamin et al.
6,579,868	B1	6/2003	Asano et al.	2004/0122228	A1	6/2004	Maier et al.
6,727,261	B2	4/2004	Gobbi et al.	2004/0126358	A1	7/2004	Warne et al.
6,784,195	B2	8/2004	Hale et al.	2004/0138214	A1	7/2004	Himmelsbach et al.
6,821,978	B2	11/2004	Chackalamannil et al.	2004/0138215	A1	7/2004	Eckhardt et al.
6,869,947	B2	3/2005	Kanstrup et al.	2004/0166125	A1	8/2004	Himmelsbach et al.
6,995,183	B2	2/2006	Hamann et al.	2004/0171836	A1	9/2004	Fujino et al.
7,060,722	B2	6/2006	Kitajima et al.	2004/0180925	A1	9/2004	Matsuno et al.
7,074,794	B2	7/2006	Kitajima et al.	2004/0259903	A1	12/2004	Boehringer et al.
7,074,798	B2	7/2006	Yoshikawa et al.	2005/0020574	A1	1/2005	Hauel et al.
7,074,923	B2	7/2006	Dahanukar et al.	2005/0026921	A1	2/2005	Eckhardt et al.
7,109,192	B2	9/2006	Hauel et al.	2005/0032804	A1	2/2005	Cypes et al.
7,179,809	B2	2/2007	Eckhardt et al.	2005/0065145	A1	3/2005	Cao et al.
7,183,280	B2	2/2007	Himmelsbach et al.	2005/0070562	A1	3/2005	Jones et al.
7,192,952	B2	3/2007	Kanstrup et al.	2005/0070594	A1	3/2005	Kauschke et al.
7,217,711	B2	5/2007	Eckhardt et al.	2005/0130985	A1	6/2005	Himmelsbach et al.
7,235,538	B2	6/2007	Kanstrup et al.	2005/0143377	A1	6/2005	Himmelsbach et al.
7,247,478	B2	7/2007	Eberhardt et al.	2005/0171093	A1	8/2005	Eckhardt et al.
7,291,642	B2	11/2007	Kauffmann-Hefner et al.	2005/0187227	A1	8/2005	Himmelsbach et al.
7,361,687	B2	4/2008	Barth et al.	2005/0203095	A1	9/2005	Eckhardt et al.
7,393,847	B2	7/2008	Eckhardt et al.	2005/0234108	A1	10/2005	Himmelsbach et al.
7,407,955	B2	8/2008	Himmelsbach et al.	2005/0234235	A1	10/2005	Eckhardt et al.
7,432,262	B2	10/2008	Eckhardt et al.	2005/0239778	A1	10/2005	Konetzki et al.
7,439,370	B2	10/2008	Eckhardt	2005/0256310	A1	11/2005	Hulin et al.
7,470,716	B2	12/2008	Eckhardt et al.	2005/0261271	A1	11/2005	Feng et al.
7,476,671	B2	1/2009	Eckhardt et al.	2005/0261352	A1	11/2005	Eckhardt
7,482,337	B2	1/2009	Himmelsbach et al.	2005/0266080	A1	12/2005	Desai et al.
7,495,002	B2	2/2009	Langkopf et al.	2005/0276794	A1	12/2005	Papas et al.
7,495,003	B2	2/2009	Eckhardt et al.	2006/0004074	A1	1/2006	Eckhardt et al.
7,495,005	B2	2/2009	Himmelsbach et al.	2006/0034922	A1	2/2006	Cheng et al.
7,501,426	B2	3/2009	Himmelsbach et al.	2006/0039974	A1	2/2006	Akiyama et al.
7,550,455	B2	6/2009	Himmelsbach et al.	2006/0047125	A1	3/2006	Leonardi et al.
7,560,450	B2	7/2009	Eckhardt et al.	2006/0058323	A1	3/2006	Eckhardt et al.
7,566,707	B2	7/2009	Eckhardt et al.	2006/0063787	A1	3/2006	Yoshikawa et al.
7,569,574	B2	8/2009	Maier et al.	2006/0074058	A1	4/2006	Holmes et al.
7,579,449	B2	8/2009	Eckhardt et al.	2006/0079541	A1	4/2006	Langkopf et al.
7,610,153	B2	10/2009	Carter, Jr. et al.	2006/0094722	A1	5/2006	Yasuda et al.
7,645,763	B2	1/2010	Himmelsbach et al.	2006/0100199	A1	5/2006	Yoshikawa et al.
7,718,666	B2	5/2010	Boehringer et al.	2006/0106035	A1	5/2006	Hendrix et al.
7,799,782	B2	9/2010	Munson et al.	2006/0111372	A1	5/2006	Hendrix et al.
7,820,815	B2	10/2010	Pfrenge et al.	2006/0111379	A1	5/2006	Guillemont et al.
7,838,529	B2	11/2010	Himmelsbach et al.	2006/0134206	A1	6/2006	Iyer et al.
8,039,477	B2	10/2011	Hendrix et al.	2006/0142310	A1	6/2006	Pfrenge et al.
8,071,583	B2	12/2011	Himmelsbach	2006/0154866	A1	7/2006	Chu et al.
8,106,060	B2	1/2012	Pfrenge et al.	2006/0159746	A1	7/2006	Troup et al.
8,119,648	B2	2/2012	Himmelsbach et al.	2006/0173056	A1	8/2006	Kitajima et al.
8,158,633	B2	4/2012	Hendrix et al.	2006/0205711	A1	9/2006	Himmelsbach et al.
8,178,541	B2	5/2012	Himmelsbach et al.	2006/0205943	A1	9/2006	Dahanukar et al.
8,232,281	B2	7/2012	Dugi et al.	2006/0247226	A1	11/2006	Himmelsbach et al.
2001/0020006	A1	9/2001	Demuth et al.	2006/0270668	A1	11/2006	Chew et al.
2001/0051646	A1	12/2001	Demuth et al.	2006/0270701	A1	11/2006	Kroth et al.
2002/0019411	A1	2/2002	Robl et al.	2007/0027168	A1	2/2007	Pfrenge et al.
2002/0137903	A1	9/2002	Ellsworth et al.	2007/0060530	A1	3/2007	Christopher et al.
2002/0161001	A1	10/2002	Kanstrup et al.	2007/0072803	A1	3/2007	Chu et al.
2002/0169174	A1	11/2002	Chackalamannil et al.	2007/0072810	A1	3/2007	Asakawa
2002/0198205	A1	12/2002	Himmelsbach et al.	2007/0088038	A1	4/2007	Eckhardt et al.
2003/0078269	A1	4/2003	Pearson et al.	2007/0093659	A1	4/2007	Bonfanti et al.
2003/0100563	A1	5/2003	Edmondson et al.	2007/0142383	A1	6/2007	Eckhardt et al.
2003/0105077	A1	6/2003	Kanstrup et al.	2007/0185091	A1	8/2007	Himmelsbach et al.
2003/0114390	A1	6/2003	Washburn et al.	2007/0196472	A1	8/2007	Kiel et al.
2003/0130313	A1	7/2003	Fujino et al.	2007/0197522	A1	8/2007	Edwards et al.
2003/0149071	A1	8/2003	Gobbi et al.	2007/0219178	A1	9/2007	Muramoto
				2007/0259900	A1	11/2007	Sieger et al.
				2007/0259925	A1	11/2007	Boehringer et al.
				2007/0259927	A1	11/2007	Suzuki et al.
				2007/0281940	A1	12/2007	Dugi et al.

(56)

References Cited

U.S. PATENT DOCUMENTS

2008/0107731 A1 5/2008 Kohlrausch et al.
 2008/0108816 A1 5/2008 Zutter
 2008/0249089 A1 10/2008 Himmelsbach et al.
 2008/0255159 A1 10/2008 Himmelsbach et al.
 2008/0312243 A1 12/2008 Eckhardt et al.
 2008/0318922 A1 12/2008 Nakahira et al.
 2009/0023920 A1 1/2009 Eckhardt
 2009/0088408 A1 4/2009 Meade et al.
 2009/0088569 A1 4/2009 Eckhardt et al.
 2009/0093457 A1 4/2009 Himmelsbach et al.
 2009/0131432 A1 5/2009 Himmelsbach et al.
 2009/0136596 A1 5/2009 Munson et al.
 2009/0137801 A1 5/2009 Himmelsbach et al.
 2009/0149483 A1 6/2009 Nakahira et al.
 2009/0186086 A1 7/2009 Shankar et al.
 2009/0192314 A1 7/2009 Pfrengle et al.
 2009/0297470 A1 12/2009 Franz
 2009/0301105 A1 12/2009 Loerting
 2009/0325926 A1 12/2009 Himmelsbach
 2010/0074950 A1 3/2010 Sesha
 2010/0092551 A1 4/2010 Nakamura et al.
 2010/0173916 A1 7/2010 Himmelsbach et al.
 2010/0179191 A1 7/2010 Himmelsbach et al.
 2010/0183531 A1 7/2010 Johncock et al.
 2010/0204250 A1 8/2010 Himmelsbach et al.
 2010/0209506 A1 8/2010 Eisenreich
 2010/0310664 A1 12/2010 Watson et al.
 2011/0009391 A1 1/2011 Braun et al.
 2011/0046076 A1 2/2011 Eickelmann et al.
 2011/0065731 A1 3/2011 Dugi et al.
 2011/0092510 A1 4/2011 Klein et al.
 2011/0098240 A1 4/2011 Dugi et al.
 2011/0112069 A1 5/2011 Himmelsbach et al.
 2011/0144083 A1 6/2011 Himmelsbach et al.
 2011/0144095 A1 6/2011 Himmelsbach et al.
 2011/0190322 A1 8/2011 Klein et al.
 2011/0195917 A1 8/2011 Dugi et al.
 2011/0206766 A1 8/2011 Friedl et al.
 2011/0263493 A1 10/2011 Dugi et al.
 2011/0263617 A1 10/2011 Mark et al.
 2011/0275561 A1 11/2011 Graefe-Mody et al.
 2011/0301182 A1 12/2011 Dugi
 2012/0003313 A1 1/2012 Kohlrausch et al.
 2012/0035158 A1 2/2012 Himmelsbach et al.
 2012/0040982 A1 2/2012 Himmelsbach et al.
 2012/0053173 A1 3/2012 Banno et al.
 2012/0094894 A1 4/2012 Graefe-Mody et al.
 2012/0107398 A1 5/2012 Schneider et al.
 2012/0121530 A1 5/2012 Klein et al.
 2012/0122776 A1 5/2012 Graefe-Mody et al.
 2012/0129874 A1 5/2012 Sieger et al.
 2012/0142712 A1 6/2012 Pfrengle et al.
 2012/0165251 A1 6/2012 Klein et al.
 2012/0208831 A1 8/2012 Himmelsbach et al.
 2012/0219622 A1 8/2012 Kohlrausch et al.
 2012/0219623 A1 8/2012 Meinicke
 2012/0252782 A1 10/2012 Himmelsbach et al.
 2012/0252783 A1 10/2012 Himmelsbach et al.
 2012/0296091 A1 11/2012 Sieger et al.
 2013/0122089 A1 5/2013 Kohlrausch et al.
 2013/0172244 A1 7/2013 Klein et al.
 2013/0184204 A1 7/2013 Pfrengle et al.
 2013/0196898 A1 8/2013 Dugi et al.
 2013/0236543 A1 9/2013 Ito et al.

FOREIGN PATENT DOCUMENTS

CA 2529729 A1 12/2004
 CA 2543074 A1 6/2005
 CA 2555050 A1 9/2005
 CA 2556064 A1 9/2005
 CA 2558067 A1 10/2005

CA 2576294 A1 3/2006
 CA 2590912 A1 6/2006
 CA 2651019 A1 11/2007
 CA 2651089 A1 11/2007
 CN 101234105 A 8/2008
 DE 2205815 A1 8/1973
 DE 2758025 A1 7/1979
 DE 10109021 A1 9/2002
 DE 10117803 A1 10/2002
 DE 10238243 A1 3/2004
 DE 102004019540 A1 11/2005
 DE 102004024454 A1 12/2005
 DE 102004044221 A1 3/2006
 DE 102004054054 A1 5/2006
 EP 0023032 A1 1/1981
 EP 0149578 A2 7/1985
 EP 0223403 A2 5/1987
 EP 0237608 A1 9/1987
 EP 0248634 A2 12/1987
 EP 0389282 A2 9/1990
 EP 0399285 A1 11/1990
 EP 0400974 A2 12/1990
 EP 409281 A1 1/1991
 EP 0412358 A1 2/1991
 EP 443983 A1 8/1991
 EP 0475482 A1 3/1992
 EP 0524482 A1 1/1993
 EP 0657454 A1 6/1995
 EP 0775704 A1 5/1997
 EP 0950658 A1 10/1999
 EP 1054012 A1 11/2000
 EP 1066265 A1 1/2001
 EP 1333033 8/2003
 EP 1338595 A2 8/2003
 EP 1406873 A2 4/2004
 EP 1500403 A1 1/2005
 EP 1514552 A1 3/2005
 EP 1535906 A1 6/2005
 EP 1537880 A1 6/2005
 EP 1557165 A1 7/2005
 EP 1586571 A1 10/2005
 EP 1743655 A1 1/2007
 EP 1760076 3/2007
 EP 1829877 A1 9/2007
 EP 1852108 A1 11/2007
 EP 1897892 A2 3/2008
 EP 2143443 A1 1/2010
 ES 385302 A1 4/1973
 ES 2256797 T3 7/2006
 ES 2263057 T3 12/2006
 FR 2707641 A1 1/1995
 GB 2084580 A 4/1982
 HU 9003243 5/1990
 HU 9902308 A2 7/2000
 JP S374895 A 6/1962
 JP 770120 3/1995
 JP 8333339 12/1996
 JP 11193270 7/1999
 JP 2000502684 A 3/2000
 JP 2001213770 A 8/2001
 JP 2002348279 A 12/2002
 JP 2003286287 A 10/2003
 JP 2003300977 A 10/2003
 JP 2004161749 A 6/2004
 JP 2006045156 A 2/2006
 JP 2010053576 A 3/2010
 JP 2010524580 A 7/2010
 KR 20070111099 A 11/2007
 WO 9107945 A1 6/1991
 WO 9205175 A1 4/1992
 WO 9219227 A2 11/1992
 WO 9402150 A1 2/1994
 WO 9403456 A1 2/1994
 WO 9532178 A1 11/1995
 WO 9609045 A1 3/1996
 WO 9611917 A1 4/1996
 WO 9636638 A1 11/1996

(56)

References Cited

FOREIGN PATENT DOCUMENTS

WO 9746526 A1 12/1997
 WO 9807725 2/1998
 WO 9811893 3/1998
 WO 9818770 A1 5/1998
 WO 9822464 A1 5/1998
 WO 9828007 A1 7/1998
 WO 9840069 A2 9/1998
 WO 9846082 A1 10/1998
 WO 9856406 A1 12/1998
 WO 9929695 A1 6/1999
 WO 9950248 A1 10/1999
 WO 9956561 A1 11/1999
 WO 9967279 A1 12/1999
 WO 0073307 A2 12/2000
 WO 0107441 A1 2/2001
 WO 0140180 A2 6/2001
 WO 0152825 7/2001
 WO 0152852 A1 7/2001
 WO 0166548 A1 9/2001
 WO 0168646 A1 9/2001
 WO 0172290 A2 10/2001
 WO 0177110 A1 10/2001
 WO 0196301 A1 12/2001
 WO 0197808 A1 12/2001
 WO 0202560 A2 1/2002
 WO 0214271 A1 2/2002
 WO 0224698 A1 3/2002
 WO 02053516 A2 7/2002
 WO 02068420 A1 9/2002
 WO 03000241 A2 1/2003
 WO 03002531 A2 1/2003
 WO 03004496 A1 1/2003
 WO 03024965 A2 3/2003
 WO 2003033686 A2 4/2003
 WO 03037327 A1 5/2003
 WO 03055881 A1 7/2003
 WO 03057200 A2 7/2003
 WO 2003053929 A1 7/2003
 WO 03064454 A1 8/2003
 WO 03088900 A2 10/2003
 WO 2003094909 A2 11/2003
 WO 03099279 A1 12/2003
 WO 03099836 A1 12/2003
 WO 03104229 A1 12/2003
 WO 03106428 A1 12/2003
 WO 2004002924 A1 1/2004
 WO 2004011416 A1 2/2004
 WO 2004016587 A1 2/2004
 WO 2004018467 A2 3/2004
 WO 2004018468 A2 3/2004
 WO 2004018469 A1 3/2004
 WO 2004028524 A1 4/2004
 WO 2004033455 A1 4/2004
 WO 2004035575 A1 4/2004
 WO 2004041820 A1 5/2004
 WO 2004046148 A1 6/2004
 WO 2004048379 A1 6/2004
 WO 2004050658 A1 6/2004
 WO 2004052362 A1 6/2004
 WO 2004058233 A1 7/2004
 WO 2004062689 A1 7/2004
 WO 2004065380 A 8/2004
 WO 2004081006 A1 9/2004
 WO 2004082402 A1 9/2004
 WO 2004096806 A1 11/2004
 WO 2004096811 A1 11/2004
 WO 2004106279 A2 12/2004
 WO 2004108730 A1 12/2004
 WO 2004111051 A1 12/2004
 WO 2005000846 A1 1/2005
 WO 2005000848 A1 1/2005
 WO 2005007647 A1 1/2005
 WO 2005007658 A2 1/2005

WO 2005049022 A2 6/2005
 WO 2005051950 A1 6/2005
 WO 2005058901 A1 6/2005
 WO 2005061489 A1 7/2005
 WO 2005063750 A1 7/2005
 WO 2005082906 A1 9/2005
 WO 2005085246 A1 9/2005
 WO 2005092870 A1 10/2005
 WO 2005092877 A1 10/2005
 WO 2005095343 A1 10/2005
 WO 2005095381 A1 10/2005
 WO 2005097798 A 10/2005
 WO 2005116000 A1 12/2005
 WO 2005116014 A1 12/2005
 WO 2005117861 A1 12/2005
 WO 2005117948 A1 12/2005
 WO 2006005613 A1 1/2006
 WO 2006027204 A1 3/2006
 WO 2006029769 A1 3/2006
 WO 2006036664 A1 4/2006
 WO 2006040625 A1 4/2006
 WO 2006047248 A1 5/2006
 WO 2006048209 A1 5/2006
 WO 2006048427 A1 5/2006
 WO 2006068163 A1 6/2006
 WO 2006071078 A1 7/2006
 WO 2006076231 A2 7/2006
 WO 2006083491 A2 8/2006
 WO 2006135693 A2 12/2006
 WO 2006137085 A1 12/2006
 WO 2007007173 A2 1/2007
 WO 2007014886 A1 2/2007
 WO 2007014895 A2 2/2007
 WO 2007017423 A1 2/2007
 WO 2007033350 A1 3/2007
 WO 2007035355 A2 3/2007
 WO 2007035665 A1 3/2007
 WO 2007041053 A2 4/2007
 WO 2007071738 6/2007
 WO 2007072083 A1 6/2007
 WO 2007078726 A2 7/2007
 WO 2007093610 A1 8/2007
 WO 2007099345 A1 9/2007
 WO 2007120702 A2 10/2007
 WO 2007120936 A2 10/2007
 WO 2007128721 A 11/2007
 WO 2007128724 A1 11/2007
 WO 2007128761 A2 11/2007
 WO 2007135196 A2 11/2007
 WO 2007137107 A2 11/2007
 WO 2007147185 A1 12/2007
 WO 2007148185 A2 12/2007
 WO 2007149797 A2 12/2007
 WO 2008005569 A2 1/2008
 WO 2008005576 A1 1/2008
 WO 2008017670 2/2008
 WO 2008022267 A2 2/2008
 WO 2008055870 A1 5/2008
 WO 2008055940 A2 5/2008
 WO 2008070692 A2 6/2008
 WO 2008081205 A1 7/2008
 WO 2008083238 A2 7/2008
 WO 2008087198 A1 7/2008
 WO 2008093878 A1 8/2008
 WO 2008093882 A1 8/2008
 WO 2008113000 A1 9/2008
 WO 2008130998 A2 10/2008
 WO 2008131149 A2 10/2008
 WO 2009011451 A 1/2009
 WO 2009022007 A1 2/2009
 WO 2009022008 A1 2/2009
 WO 2009022010 A1 2/2009
 WO 2009024542 A2 2/2009
 WO 2009063072 A2 5/2009
 WO 2009099734 A1 8/2009
 WO 2009112691 A2 9/2009
 WO 2009121945 A2 10/2009

(56)

References Cited

FOREIGN PATENT DOCUMENTS

WO	2010015664	A1	2/2010
WO	2010018217	A2	2/2010
WO	2010029089	A2	3/2010
WO	2010043688	A1	4/2010
WO	2010045656	A2	4/2010
WO	2010072776	A1	7/2010
WO	2010079197	A1	7/2010
WO	2010086411	A1	8/2010
WO	2010092124	A1	8/2010
WO	2010092125	A1	8/2010
WO	2010092163	A2	8/2010
WO	2010096384	A2	8/2010
WO	2010106457	A2	9/2010
WO	2010147768	A1	12/2010
WO	2011039337	A1	4/2011
WO	2011039367	A2	4/2011
WO	2011064352	A1	6/2011
WO	2011113947	A1	9/2011
WO	2011138380	A1	11/2011
WO	2011138421	A1	11/2011
WO	2011161161	A1	12/2011
WO	2012031124	A2	3/2012
WO	2012065993	A1	5/2012
WO	2012106303	A1	8/2012
WO	2012120040	A1	9/2012
WO	2013098372	A1	7/2013
WO	2013103629	A1	7/2013

OTHER PUBLICATIONS

Januvia; Patient Information; 2010.

Kanada, S. et al., "Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple doses of BI 1356 (proposed tradename Ondero), a dipeptidyl peptidase 4 inhibitor, in Japanese patients with type 2 diabetes" *Diabetes*, vol. 57, No. Suppl. 1, Jun. 2008, p. A158-A159 and 68th Annual Meeting of the American Diabetes Association: San Francisco, CA, Jun. 6-10, 2008.

Kim, D. et al., "(2R)-4-oxo-4-(3-(Trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-1-(2,4,5-trifluorophenyl)butan-2-amine: A Potent, Orally Active Dipeptidyl Peptidase IV inhibitor for the Treatment of Type 2 Diabetes." *Journal Med. Chem.* 2005, 48, p. 141-151.

Korom, S. et al; Inhibition of CD26/dipeptidyl peptidase IV activity in vivo prolongs cardiac allograft survival in rat recipients 1,2, *Transplantation*, May 27, 1997, vol. 63, No. 10, pp. 1495-1500.

Lambier, A.M. et al., Dipeptidyl-Peptidase IV from Bench to Bedside: An Update on Structural Properties, Functions, and Clinical Aspects of the Enzyme DPP IV. *Critical Reviews in Clinical Laboratory Sciences*, 2003, 40(3), p. 209-294.

March, J. "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure". Fourth Edition, 1992, pp. 652-653.

Mendes, F.D, et al. "Recent advances in the treatment of non-alcoholic fatty liver disease". *Expert Opinion on Investigational Drugs*, vol. 14, No. 1, Jan. 1, 2005, p. 29-35.

Merck: "Initial Therapy with Janumet (sitagliptin/metformin) provided significantly greater blood sugar lowering compared to metformin alone in patients with type 2 diabetes". *Webwire.com*, Jun. 8, 2009, p. 1-4. <http://www.webwire.com/ViewPressRel.asp?ald=96695>.

O'Farrell, et al., "Pharmacokinetic and Pharmacodynamic Assessments of the Dipeptidyl Peptidase-4 Inhibitor PHX1149: Double-Blind, Placebo-controlled, Single-and Multiple-Dose Studies in Healthy Subjects". *Clinical Therapeutics, Excerpta Medica*, Princeton, NJ, vol. 29, No. 8, 2007, p. 1692-1705.

Patani George A. et al.: "Bioisoterism : A Rational Approach in Drug Design", *Chemical Reviews*, 1996, vol. 96, No. 8, pp. 3147-3176.

Pei, Z.: "From the bench to the bedside: Dipeptidyl peptidase IV inhibitors, a new class of oral antihyperglycemic agents" *Current*

Pospasilik, et al; Dipeptidyl Peptidase IV Inhibitor Treatment Stimulates ? -Cell Survival and Islet Neogenesis in Streptozotocin-Induced Diabetic Rats; Diabetes, vol. 52, Mar. 2003 pp. 741-750.

Priimenko, B. A., et al; Synthesis and Pharmacological Activity of Derivates of 6,8-Dimethyl Imidazo(1,2-f) Xanthine-(Russ.); *Khimiko-Farmatsevicheskii zhurnal* (1984) vol. 18, No. 12 pp. 1456-1461.

Rhee et al: "Nitrogen-15-Labeled Deoxynucleosides. 3. Synthesis of [3-15N]-2'-Deoxyadenosine" *J. Am. Chem. Soc.* 1990, 112, 8174-8175.

Rosenstock, et al., "Efficacy and tolerability of initial combination therapy with vildagliptin and pioglitazone compared with component monotherapy in patients with type 2 diabetes". *Diabetes, Obesity and Metabolism*, Mar. 2007, vol. 9, No. 2, p. 175-185.

Salomon, J., et al; Ultraviolet and g-Ray-Induced Reactions of Nucleic Acid Constituents. *Reactions of Purines with Amines; Photochemistry and Photobiology* (1974) vol. 19 pp. 21-27.

Sathananthan, A., et al., "Personalized pharmacotherapy for type 2 diabetes mellitus". *Personalized Medicine 2009 Future Medicine Ltd*, vol. 6, No. 4, Jul. 2009, p. 417-422.

Sauer, R, et al. "Water-soluble phosphate prodrugs of 1-Propargyl-7-styrylxanthine derivatives, A2A-selective adenosine receptor antagonists". *Journal Med. Chem.*, vol. 43, Issue 3, Jan. 2000, p. 440-448.

Schwartz, M. S. et al., "Type 2 Diabetes Mellitus in Childhood: Obesity and Insulin Resistance". *JAOA Review Article*, vol. 108, No. 9, Sep. 2008, p. 518.

Scientific Discussion: "Eureas. Scientific discussion". Online Oct. 2007, p. 1-27, URL:<http://www.emea.europa.eu/humandocs/PDFs/EPAR/eureas/H-807-en6.pdf>. see point 2. quality aspects pp. 2-4. (EMA).

Sedo, A. et al; "Dipeptidyl peptidase IV activity and/or structure homologs: Contributing factors in the pathogenesis of rheumatoid arthritis?" *Arthritis Research & Therapy* 2005, vol. 7, pp. 253-269.

Stahl, P.H., "Handbook of Pharmaceutical Salts". C.G. Wermuth, Wiley-VCH, 2002, p. 61.

Tamm, E, et al., "Double-blind study comparing the immunogenicity of a licensed DTwPHib-CRM197 conjugate vaccine (Quattvaxem TM) with three investigational, liquid formulations using lower doses of Hib-CRM197 conjugate". *Science Direct, Vaccine*, Feb. 2005, vol. 23, No. 14, p. 1715-1719.

Tanaka, S., et al; "Suppression of Arthritis by the Inhibitors of Dipeptidyl Peptidase IV;" *In. J. Immunopharmac.*, vol. 19, No. 1, pp. 15-24, 1997.

World Health Organization (WHO). "Addendum 1 to "The use of stems in the selection of International Nonproprietary names (INN) for pharmaceutical substances"" Online Jun. 19, 2007, pp. 1-3, retrieved from URL: <http://www.who.int/medicinedocs/index/assoc/s1414e/s1414e.pdf>.

X-Ray Diffraction. *The United States Pharmacopeia*, 2002, USP 25 NF20, p. 2088-2089.

Yasuda, et al. "E3024 3-but-2-ynyl-5-methyl-2-piperazin-1-yl-3,5-dihydro-4H-imidazol [4,5-d]pyridazin-4-one tosylate, is a move, selective and competitive dipeptidyl peptidase-IV inhibitor". *European Journal of Pharmacology*, vol. 548, No. 1-3, Oct. 24, 2006, p. 181-187. Abstract.

Yoshikawa, Seiji et al.: *Chemical Abstract of Japanese Patent No. WO 2003/104229 Preparation of purinone derivatives as dipeptidylpeptidase IV (DPP-IV) inhibitors*, 2003.

Zeje, Alfred, et al; "Badania Nad Piperazynowymi Pochodnymi Dwumetyloksantyn" *Acta Polon Pharm*, XXXV (1976) Nr. 4 pages 417-421.

Zhong, Qing et al; "Glucose-dependent insulinotropic peptide stimulates proliferation and TGF-? release from MG-63 cells," *Peptides* 24 (2003) 611-616.

Zimmer et al; Synthesis of 8-Substituted Xanthines and their Oxidative Skeleton Rearrangement to 1-0xo-2,4,7,9-tetraazaspiro[4,5]dec-2-ene-6,8,10-triones; *European Journal Organic Chemistry* (1999) vol. 9 pp. 2419-2428.

Abstract in English for German DE2205815, 1972.

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.