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A Review of the Delamanid Patent Landscape

A scoping report

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CONTENTS

1. INTRODUCTION

The World Health Organization (WHO) estimates that a third of the world's population is latently infected with *Mycobacterium tuberculosis*. In 2012, there were an estimated 8.6 million incident cases of tuberculosis (TB), with 12 million prevalent cases, 940 000 deaths among HIV-negative people, and 320 000 deaths among HIV-positive people.[1] Most cases (58%) were in the WHO South-East Asia and Western Pacific regions, while the WHO African Region had 27% of the world's cases. Despite being curable, TB claimed the lives of 1.3 million people in 2012.

TB treatment has become more complex, particularly with the emergence of multidrug-resistant (MDR) strains of *Mycobacterium tuberculosis*. There were approximately 450 000 new cases of multidrug-resistant tuberculosis (MDR-TB) worldwide in 2012.[1] MDR-TB is resistant to the two most commonly used TB drugs, isoniazid and rifampicin. It requires extended treatment with second-line drugs that are less effective and have more adverse effects than isoniazid- and rifampicin-based regimens.[2]

Given the emergence of MDR-TB and the need to shorten treatment duration, new drugs are required. The last of the current anti-TB treatments—rifampicin—was introduced in 1963. Since then, research for new TB treatments had largely come to a halt. However, in recent years the pipeline for potential new TB treatments has started to look more promising than it has for the past 50 years.

One compound of interest is Otsuka Pharmaceutical's delamanid (OPC 67683). Delamanid has been identified as a possible new treatment for MDR-TB.[3] In November 2013, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency granted a conditional marketing authorization for delamanid, which is marketed under the brand name Deltyba, for the treatment of MDR-TB.

In view of delamanid's potential role in the treatment of MDR-TB, this report explores the patent landscape and considers possible access issues relating to this drug.

1 Global tuberculosis report 2013. Geneva: World Health Organization; 2013 (http://www.who.int/tb/publications/global_report/en/, accessed 31 December 2013).

2 Diacon A et al. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. New England Journal of Medicine. 2009;360:2397-2405.

3 Gler MT et al. Delamanid for multidrug-resistant pulmonary tuberculosis. New England Journal of Medicine. 2012;366:2151-2160.

2. BACKGROUND

Delamanid was discovered via a screening programme carried out by Otsuka. The compound belongs to the nitroimidazole class of compounds and is a derivative of compound CGI-17341 whose anti-TB activity was already reported in 1993.[4] Indeed, various 5- and 2-nitroimidazoles and 5-nitrofurans were already known to be effective against a variety of protozoan and bacterial infections in humans and animals.[5] For example, the published international patent application WO 97/01562 previously disclosed a 6-nitro-1,2,3,4-tetrahydro[2,1-b]-imidazopyran compound with bactericidal action in vitro to mycobacterium TB.

Previously known as OPC-67683, delamanid is a mycolic-acid biosynthesis inhibitor found to be free of mutagenicity and to possess highly potent activity against TB, including MDR-TB.[6] Compared to the earlier nitroheterocyclic compounds that were disclosed in international patent application WO 97/01562, delamanid is considered to differ structurally in terms of its basic skeleton and mutagenic properties.

Chemical names for delamanid are:

- imidazo[2,1-*b*]oxazole, 2,3-dihydro-2-methyl-6-nitro-2-[[4-[4-[4- (trifluoromethoxy)phenoxy]-1-piperidinyl]phenoxy]methyl]-, (2*R*)-; and
- (2*R*)-2-methyl-6-nitro-2-[(4-{4-[4-(trifluoromethoxy)phenoxy]piperidin-1- yl}phenoxy)methyl]-2,3-dihydroimidazo[2,1-*b*]oxazole.

The structure of delamanid is shown in Figure 1.

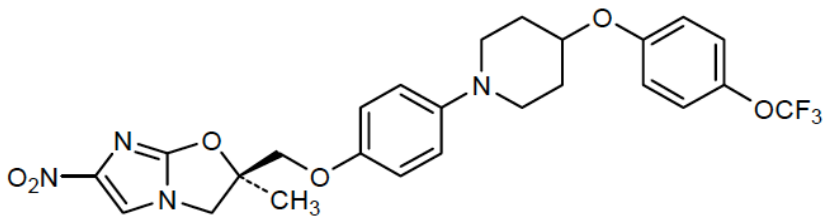

Figure 1. Structure of delamanid

Delamanid is currently in Phase III clinical trials to determine whether it is effective in the treatment of MDR-TB in combination with other MDR-TB medications during six months of treatment.[7] Trials are being conducted in Estonia, India, Latvia, Lithuania, Peru, Philippines, Republic of Moldova and South Africa. However, at the end of 2011, Otsuka filed for approval of delamanid in relation to MDR-TB at the European Medicines Agency (EMA). According to reports, Otsuka has received approval from the EMA for paediatric testing.[8] Paediatric trials are also reportedly taking place in Philippines and South Africa.[9] While conditional marketing approval for the adult formulation has been granted in Europe, it is not yet clear when a paediatric version will enter the market.

4 Ashtekar DR et al. In vitro and in vivo activities of the nitroimidazole CGI 17341 against Mycobacterium tuberculosis. Antimicrobial Agents and Chemotherapy. 1993;37(2):183-186.
5 Raether W et al. Nitroheterocyclic drugs with broad spectrum activity. Parasitol Research. 2003;90:S19-39.
6 Matsumoto M et al. OPC-67683, a nitro-dihydro-imidazooxazole derivative with promising action against tuberculosis in vitro and in mice. PLOS Medicine. 2006;3(11):2131-2144.
7 See: Safety and efficacy trial of delamanid for 6 months in patients with multidrug resistant tuberculosis (http://clinicaltrials.gov/show/NCT01424670, accessed 31 December 2013).
8 Mazzotta M. Top private funder of TB R&D moves forward with trials of promising new drug. Science Speaks: HIV & TB News; 21 March 2012 (http://sciencespeaksblog.org/2012/03/21/top-funder-of-tb-rd-moves-forward-with-trials-of-promising-new-drug/#axzz2KF0rJsIl, accessed 31 December 2013).
9 See: A 6-month safety, efficacy, and pharmacokinetic trial of delamanid in pediatric patients with multidrug resistant tuberculosis (http://clinicaltrials.gov/ct2/show/NCT01859923, accessed 31 December 2013).

3. DELAMANID: THE PATENT LANDSCAPE

The patent landscape in Annex I of this report sets out the key patents and patent applications for delamanid, including their geographical patent coverage, as of February 2013. While every effort has been made to obtain comprehensive and accurate information on the status and geographical scope of the patents covering delamanid, in many countries patent information is not readily available to the public or not updated on a regular basis. In addition, some patent applications may have been published only after the searches were conducted. As such, there may be other relevant patents which have subsequently been published and which are not included in this landscape. Accordingly, the information provided herein is subject to the above disclaimers.

Patent searches identified nine relevant patents. For ease of reference these nine patents have been identified as Patents 1–9 in Annex I. All the patents were filed and remain in the name of Otsuka Pharmaceutical Co. Ltd.

Patent 1 covers various 2,3-dihydro-6-nitroimidazo 2,1-b oxazole compounds, including the base compound delamanid, its racemates and isomers. The information available for Patent 1 is limited in terms of whether there is patent coverage in all high-burden TB and MDR-TB countries, particularly in Africa. However, key countries where the patent has been granted to date include China, India, Philippines and Russia. A divisional patent deriving from the granted patent is also pending in India. The international patent application has also entered the national phase in Egypt, Indonesia, Pakistan, South Africa, Ukraine and Viet Nam, but further checks are required to determine the current status of the applications.

Patent 2 covers a broad range of 2,3-dihydro-6-nitroimidazo 2,1-b oxazole compounds for the treatment of TB, including their optically active forms. The coverage of this patent overlaps with that claimed in Patent 1 and includes protection for delamanid in claim 1. The information available for Patent 2 is limited in terms of whether there is patent coverage in all high-burden TB and MDR-TB countries, particularly in Africa. However, key countries where the patent has been granted to date include China, Philippines and Russia. The international patent application has also entered the national phase in Egypt, India, Indonesia, Pakistan, South Africa, Thailand, Ukraine and Viet Nam. With the exception of India, where the patent is awaiting examination, further checks are required to determine the current status of the applications in the other countries.

Patent 3 covers a broad range of pharmaceutical compositions for formulation purposes, comprising at least one 2,3-dihydro-6-nitroimidazo 2,1-b oxazole compound, hydroxypropylmethyl cellulose phthalate or acetate succinate. The information available for Patent 3 is limited in terms of whether there is patent coverage in all high-burden TB and MDR-TB countries, particularly in Africa. However, key countries where the patent has been granted to date include China, India, Philippines, Russia and Ukraine. The international patent has also entered the national phase in Egypt, Indonesia, Pakistan, South Africa, Thailand and Viet Nam. Further checks are required to determine the current status of the applications in these countries.

Patent 4 covers a broad range of pharmaceutical compositions comprising at least one 2,3-dihydro-6-nitroimidazo 2,1-b oxazole compound in combination with other antituberculosis drugs, including isoniazid, ethambutol, streptomycin, pyrazinamide, enviomycin, kanamycin, capreomycin, cycloserine, thioacetazone, clofazimine, rifampicin and moxifloxacin. The information available for Patent 4 is limited in terms of whether there is patent coverage in all high-burden TB and MDR-TB countries, particularly in Africa. However, key countries where there is information confirming the international patent application entering the national phase include China, India, Egypt, India, Philippines, South Africa and Russia. With the exception of China and India, where the patent applications are still pending, further checks are required to determine the current status of the applications in the other countries.

Patent 5 covers a pharmaceutical composition comprising delamanid, a fatty acid and organic acid glycerol ester and/or a fatty acid and organic acid polyglycerol ester. The information available for Patent 5 is limited in terms of whether there is patent coverage in all high-burden TB and MDR-TB countries, particularly in Africa. This could be due to a delay in publication of the national phase data for the international patent application.

Patent 6 covers synthetic intermediate compounds that are useful for producing an oxazole compound, including delamanid, at a high yield and high optical purity. The information available for Patent 6 is limited in terms of whether there is patent coverage in all high-burden TB and MDR-TB countries, particularly in Africa. This could be due to a delay in publication of the national phase data for the international patent application. The data available shows that the application is pending in China.

Patent 7 covers early nitroimidazole compounds and methods of their preparation as early intermediates. The compounds relate to earlier uses discussed in international patent WO 97/01562, as noted above. The information available for Patent 7 is limited in terms of whether there is patent coverage in all high-burden TB and MDR-TB countries, particularly in Africa. However, key countries where the patent has been granted to date include China, India, Philippines, Russia and Ukraine. The international patent application has entered the national phase in Egypt, Indonesia, Pakistan, Thailand, South Africa and Viet Nam. Further checks are required to determine the current status of the applications in these countries.

Patent 8 covers a method for preparing nitroimidazole compounds as early intermediates. This patent relates closely to WO 2004/035547 (Patent 7). The information available for Patent 8 is limited in terms of whether there is patent coverage in all high-burden TB and MDR-TB countries, particularly in Africa. However, key countries where the patent has been granted to date include China, India, Philippines, Russia and Ukraine. The international patent application has entered the national phase in Egypt, Indonesia, Pakistan, Thailand, South Africa and Viet Nam. Further checks are required to determine the current status of the applications in these countries.

Patent 9 covers a process for producing aminophenol compounds, which could act as intermediates for producing nitroimidazole compounds. The information available for Patent 9 is limited in terms of whether there is patent coverage in all high-burden TB and MDR-TB countries, particularly in Africa. However, key countries where the patent has been granted to date include China, India, Philippines and Russia. The international application has entered the national phase in Egypt, Indonesia, Pakistan, South Africa and Viet Nam. Further checks are required to determine the current status of the applications in these countries.

4. CONCLUSION

As this analysis shows, patents and patent applications for delamanid are already in place in a number of key countries, including several which may have local manufacturing capability and have a high burden of MDR-TB. While not all the patent applications identified may be pursued and/or granted, this nevertheless indicates that patents may in future become more important in determining access to TB treatment.

Determining the patent situation is a useful starting point for understanding the possible access issues, since patents can bar competitors from manufacturing, selling, importing or exporting a product.[10] Moreover, although only a granted patent can actually bar competition, patent applications serve as a deterrent.

Nevertheless, competition and access to medicines are not determined exclusively by patents but also by, among other things, the patent-holder's licensing strategies and/or access programme. At the time of writing there was little public information on Otsuka's policy for access to delamanid, or on its envisaged pricing strategy. According to reports, Otsuka has stated that it will take a cautious approach in order to preserve delamanid's potency for treating MDR-TB.[11]

10 Companies typically file their patents in a manner that enables them to control access to a drug in key developing-country markets (usually middle-income economies); this includes filing in countries where there is a risk of generic competitors being able to produce the drug locally.

11 Matsuyama K. First tuberculosis drug in 40 years has Otsuka cautious. Bloomberg News. 7 June 2012 (http://www.bloomberg.com/news/2012-06-06/stalling-sales-may-give-otsuka-edge-with-cure-for-tb-superbugs.html, accessed 31 December 2013). See also note 8, above.

ANNEX I: DELAMANID (OPC-67683) PATENT LANDSCAPE

Patents 1–6 have been identified as the key patents and have therefore been listed first, instead of using a chronological order based on filing date. Patent searches were conducted in February 2013.

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5
	2,3-dihydro-6-nitroimidazo [2, 1-b] oxazoles ***(This patent covers various compounds, including delamanid and its racemates and single isomers)***	**2,3-dihydro-6-nitroimidazo [2, 1-b] oxazole compounds for the treatment of tuberculosis** ***(This patent covers various compounds, including delamanid)***	**Pharmaceutical composition comprising 2,3-dihydro-6-nitroimidazo [2, 1-b] oxazole derivatives** ***(This patent covers a pharmaceutical composition comprising delamanid, its optically active isomers and pharmaceutically acceptable salts, with a cellulose compound)***	**Antituberculous composition comprising oxazole compounds** ***(This patent covers delamanid in combination with other antituberculous drugs, including rifamycin, isoniazid, ethambutol, streptomycin, pyrazinamide, enviomycin and kanamycin)***	**Medicinal composition showing improved drug absorbability** ***(This patent covers a pharmaceutical composition comprising delamanid and a fatty acid and organic acid glycerol ester and/or a fatty acid and organic acid polyglycerol ester)***
Applicant	**Otsuka Pharmaceutical Co. Ltd**	**Otsuka Pharmaceutical Co. Ltd**	**Otsuka Pharmaceutical Co. Ltd**	**Otsuka Pharmaceutical Co. Ltd**	**Otsuka Pharmaceutical Co. Ltd**
International Patent Publication No.	**WO 2004/033463**	**WO 2005/042542**	**WO 2007/013477**	**WO 2007/043542**	**WO 2007/052738**
Expected expiry (if granted and not subject to patent term extensions)	**9 October 2023**	**28 October 2024**	**18 July 2026**	**3 October 2026**	**1 November 2026**
	PATENT STATUS				
Argentina	Current status not available Pub No.041198 App No. P030103673	Current status not available Pub No. 046777 App No. P040103961	Current status not available Pub No. 055357 App No. P060103282	Current status not available Pub No. 056872 App No. P060104358	Current status not available Pub No. 05783 App No. P060104810
Australia	Granted Patent No. 2003272979 Pub/App No. 2003272979	Granted Patent No. 2004285811 Pub/App No. 2004285811	Granted Patent No. 2006273355 Pub/App No. 2006273355	Granted Patent No. 2006300320 Pub/App No. 2006300320	NA
				Pending Pub/App No. 20100241497	

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5
Bangladesh	Current status not available App No. 258/2003	Current status not available App No. 263/2004	Current status not available App No. 164/2006	NA	NA
Belarus	Current status not available App No. A20050451	Current status not available App No. A20060534	Granted Patent No. 14174 App No. A20080226	NA	NA
Brazil	Pending Pub/App No. PI0314344-9	Pending Pub/App No. PI0414909-2	Pending Pub/App No. PI0613883-7	NA	NA
Canada	Granted Patent No. 2497569 Pub/App No. 2497569	Pending Pub/App No. 2539335	Pending Pub/App No. 2610749	Pending Pub No. 2624497 App No. 20062624497	NA
China	Granted Patent No. 100366624 Pub No. 1705670 App No. 200380101750.8	Granted Patent No. 100497345 Pub No. 1878777 App No. 20048032244	Granted Patent No. 101222913 Pub No. 101222913 App No. 200680025866	Pending Pub No. 101277740 App No. 20068036787	NA
	Pending Pub No. 101172981 App No. 200710004036				
	Pending Pub No. 101255170 App No. 2200710004037				
	Pending Pub No. 102532162 App No. 20111416170				
China, Hong Kong SAR	Current status not available Pub No. 1085463 App No. 06101486.3	Current status not available Pub No. 1097258 App No. 20070101546	Granted Patent No. 1114565 Pub No. 1114565 App No. 20080110119	NA	NA
Egypt	Current status not available App No. 113/2005	Current status not available App No. 401/2006	Current status not available App No. 2008010154	Current status not available App No. 2008040571	NA
European Patent Office	Pending Pub No. 1555267 App No. 03754085.3	Granted Patent No. 1678185 Pub No. 1678185 App No. 04793412	Granted Patent No. 1906926 Pub No. 1906926 App No. 06781620.7	Pending Pub No. 1931425 App No. 060811551	No Application Found

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5
India	Granted Patent No. 250365 Pub/App No. 600/KOLNP/2005	Pending Pub/App No. 824/KOLNP/2006	Granted Patent No. 253642 Pub/App No. 9790/DELNP/2007	Pending Pub/App No. 1255/KOLNP/2008	No Application Found
	Pending Pub/App No. 1647/KOLNP/2007				
Indonesia	Current status not available App No. WO0200500873	Current status not available App No. WO0200601150	Current status not available Pub No. 048.2242A App No. WO0200800233	NA	NA
Israel	NA	NA	NA	Current status not available Pub/App No. 189944	NA
Japan	Granted Patent No. 4186065 Pub No. 2004149527 App No. 20030353868	Granted Patent No. 4761756 Pub No. 2005320316 App No. 20040318005	Granted Patent No. 4808246 Pub No. 2009502736 App No. 20080504290	Pending Pub No. 2007126452 App No. 20060273707	Pending App No. 2007542799
Malaysia	Current status not available Pub No. 139244 App No. PI20033866	Current status not available App No. PI20044505	Granted Patent No. 144554-A App No. PI20063579	NA	NA
Mexico	Current status not available App No. PA/A/2005/003674	Current status not available App No. PA/A/2006/004064	Granted Patent No. 282814 Pub/App No. MX/a/2008/001210	Current status not available App No. MX/a/2008/004256	NA
Pakistan	Current status not available App No. 888/2003	Current status not available App No. 860/2004	Current status not available App No. 826/06	NA	NA
	Current status not available App No. 1308/2006	Current status not available App No. 1225/2006			
Philippines	Granted Patent No. 12005500439 Pub/App No. 12005500439	Granted Patent No. 12006500783 Pub/App No.12006500783	Granted Patent No. 12007502673 Pub/App No. 12007502673	Pending App No. 12008500603	NA
Poland	Current status not available Pub No. 376157 App No. 200376157	NA	NA	NA	NA

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5
Republic of Korea	Granted Patent No. 100723847 Pub No. 20050061473 App No. 10-2005-7004567	Granted Patent No. 100851802 Pub No. 20060085664 App No. 20067006629	Pending Pub No. 20080033458 App No. 20087004656	Granted Patent No. 101118942 Pub No. 20080052648 App No. 20087008171	NA
Russia	Granted Patent No. 2326121 Pub/App No. 2005114017	Granted Patent No. 2365593 Pub/App No. 2006118794	Granted Patent No. 2413504 Pub/App No. 2008107595	Pending Pub/App No. 2008117427	NA
Singapore	Pending App No. 200503468-1	Pending App No. 200601851-9	Granted Patent No. 137570 Pub/App No. 200718046-6	Pending Pub No. 165361 App No. 20100006561	NA
Slovenia	NA	Current status not available Pub No. 1678185 App No. 20040030914	Current status not available Pub No. 1906926 App No. 20060030877	NA	NA
South Africa	Current status not available App No. 2005/01033	Current status not available App No. 200602184	Current status not available App No. 2007001404	Current status not available App No. 20080002883	NA
Taiwan, China	Current status not available Pub No. 200420568 App No. 92128165	Granted Patent No. 335331 Pub/App No. 20040132982	Current status not available Pub No. 200727917 App No. 95126526	NA	Current status not available Pub No. 200800268 App No. 20060140012
Thailand	Current status not available App No. 085817	Current status not available App No. 095004	Current status not available Pub No. 88205 App No. 0601003519	NA	NA
Ukraine	Current status not available App No. A200504391	Pending App No. A200605975	Granted Patent No. 95251 Pub/App No. 200802496	NA	NA
USA	Granted Patent No. 7262212 Pub No. 2006094767 App No. 10/530429	Granted Patent No. 8163753 Pub No. 2008119478 App No. 10/574597	Granted Patent No. 7943623 Pub No. 2010130508 App No. 11/996699	Pending Pub No. 2009275528 App No. 12/088867	Pending Pub No. 2009227630 App No. 12/084483
Viet Nam	Current status not available App No. 1200500622	Current status not available App No. 1200600645	Current status not available App No. 1200800490	NA	NA

NA: Patent information not available at the time the patent searches were conducted (February 2013).

	Patent 6	Patent 7	Patent 8	Patent 9
	Synthetic intermediate of oxazole compound and method for producing the same ***(This patent covers new synthetic intermediate compounds useful for producing an oxazole compound, including delamanid, at a high yield and high optical purity)***	**1-Substituted 4-nitroimidazole compound and process for producing the same** ***(This patent covers nitroimidazole compounds and methods of their preparation as early intermediates)***	**Method for producing 4-nitroimidazole compound** ***(This patent covers a method for preparing nitroimidazole compounds as early intermediates. This patent relates closely to WO 2004/035547)***	**Method of producing aminophenol compounds** ***(This patent covers a process for producing aminophenol compounds, which could act as intermediates in relation to nitroimidazole compounds)***
Applicant	**Otsuka Pharmaceutical Co. Ltd**	**Otsuka Pharmaceutical Co. Ltd**	**Otsuka Pharmaceutical Co. Ltd**	**Otsuka Pharmaceutical Co. Ltd**
International Patent Publication No.	**WO 2011/093529**	**WO 2004/035547**	**WO 2005/077913**	**WO 2005/092832**
Expected expiry (if granted and not subject to patent term extensions)	**27 January 2031**	**14 October 2023**	**15 February 2025**	**25 March 2025**
	PATENT STATUS			
Argentina	Current status not available Pub No. 080287 App No. P0110100285	Current status not available Pub No. 041605 App No. P030103730	Current status not available Pub No. 047672 App No. P050100523	Current status not available Pub No. 048043 App No. P050101090
Australia	Pending Pub/App No. 2011211311	Granted Patent No. 2003301282 Pub/App No. 2003301282	Granted Patent No. 2005212093 Pub/App No. 2005212093	Granted Patent No. 2005226409 Pub/App No. 2005226409
Bangladesh	NA	Current status not available App No. 261/2003	Current status not available App No. 43/2005	Current status not available App No. 75/2005
Belarus	NA	Current status not available App No. 20050456	Current status not available App No. 20060909	Current status not available App No. 20061039
Brazil	NA	Pending Pub/App No. PI0313566-7	Pending Pub/App No. PI0507777-0	Pending Pub/App No. PI0509095-4
Canada	Pending Pub No. 2787246 App No. 20112787246	Granted Patent No. 2494710 Pub/App No. 2494710	Pending Pub/App No. 2555372	Granted Patent No. 2559488 Pub/App No. 2559488

	Patent 6	Patent 7	Patent 8	Patent 9
China	Pending Pub No. 102725269 App No. 20118006814	Granted Patent No. 1326840 Pub No. 1692103 App No. 20038100667	Granted Patent No. 100526300 Pub No. 1922154 App No. 20058005310	Granted Patent No. 100478325 Pub No. 1938261 App No. 20058009653
China, Hong Kong SAR	NA	Current status not available Pub No. 1083830 App No. 20060103740	Current status not available Pub No. 1097846 App No. 20070104279	Current status not available Pub No. 1097823 App No. 20070104267
Egypt	NA	Current status not available Pub No. 24885 App No. 20005000131	Current status not available Pub No. 24393 App No. 20006000764	Current status not available Pub No. 25686 App No. 20006000821
European Patent Office	NA	Pending Pub No. 1553088 App No. 20030756610	Granted Patent No. 1720838 Pub No. 1720838 App No. 20050710450	Granted Patent No. 1727782 Pub No. 1727782 App No. 20050727512
India	NA	Granted Patent No. 219525 Pub/App No. 605/KOLNP/2005	Granted Patent No. 248249 Pub/App No. 2205/KOLNP/2006	Granted Patent No. 244643 Pub/App No. 2585/KOLNP/2006
Indonesia	NA	Current status not available App No. WO0200500908	Current status not available App No. WO0200602294	Current status not available App No. WO0200602656
Israel	Current status not available App No. 220754	NA	NA	NA
Japan	NA	Granted Patent No. 4258630 Pub No. 2004269500 App No. 20030354575	Granted Patent No. 4789483 Pub No. 2006117628 App No. 20050042010	Granted Patent No. 4761802 Pub No. 2005306866 App No. 20050089215
		Granted Patent No. 5014315 Pub No. 2009102329 App No. 20080305239		
Malaysia	NA	Current status not available Pub No. 145079 App No. PI2003919	Current status not available Pub No. 141776 App No. PI20050484	Current status not available Pub No. 143665 App No. PI20051053
Mexico	NA	Current status not available Pub/App No. 05002414	Current status not available Pub/App No. 06009262	Current status not available Pub/App No.06010967
Pakistan	NA	Current status not available App No. 893/2003	Current status not available App No. 59/2005	Current status not available App No. 173/2005

	Patent 6	Patent 7	Patent 8	Patent 9
Philippines	NA	Granted Patent No. 2009500934 Pub/App No. 2009500934	Granted Patent No. 12006501555 Pub/App No. 12006501555	Granted Patent No. 12006501783 Pub/App No. 12006501783
		Granted Patent No. 2005500235 Pub/App No. 2005500235		
		Current status not available Pub/App No. 2010502766		
Republic of Korea	NA	Granted Patent No. 100655670 Pub No. 20050046013 App No. 20057006493	Granted Patent No. 100830386 Pub No. 20060116857 App No. 20067017553	Granted Patent No. 100766763 Pub No. 20060123650 App No. 20067019609
Russian Federation	NA	Granted Patent No. 2324682 Pub/App No. 2005114534	Granted Patent No. 2345071 Pub/App No. 20060133312	Granted Patent No. 2376280 Pub/App No. 20060137563
Singapore	NA	Current status not available App No. 200501125-9	Current status not available App No. 200605139-5	Current status not available App No. 200606095-8
South Africa	NA	Current status not available Pub/App No. 2005/0918	Current status not available Pub/App No. 2006/06332	Current status not available Pub/App No. 2006/07640
Taiwan, China	Current status not available Pub No. 201200523 App No. 100102823	Granted Patent No. 331607 Pub/App No. 20030128442	Granted Patent No. 300409 Pub/App No. 20050103101	Current status not available Pub/App No. 200531958
		Current status not available Pub No. 200838855 App No. 20080117703		
Thailand	NA	Current status not available App No. 085911	Current status not available App No. 0501000611	NA
Ukraine	NA	Granted Patent No. 80839 Pub/App No. 200503528	Granted Patent No. 82773 Pub/App No. 20060010008	NA

	Patent 6	Patent 7	Patent 8	Patent 9
USA	NA	Granted Patent No. 7368579 Pub No. 2006079697 App No. 10/523,008	Granted Patent No. 7569702 Pub No. 2007161802 App No. 10/589,864	Granted Patent No. 7750156 Pub No. 2007219374 App No. 10/593,968
		Granted Patent No. 7807843 Pub No. 2008200689 App No. 12/007,776		
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Viet Nam		Current status not available App No. 1200500461	Current status not available App No. 1200601519	Current status not available App No. 1200601751

NA: Patent information not available at the time the patent searches were conducted (February 2013).