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A Review of the AZD5847 Patent Landscape

A scoping report

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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 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 that is currently in the pipeline and generating interest is AstraZeneca's investigational compound AZD5847. AZD5847 has been identified as a possible new treatment for drug-susceptible TB and/or for MDR-TB.

Given the potential of AZD5847, this report explores the patent landscape and considers possible access issues relating to the drug should it become available on the market.

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.

2. BACKGROUND

AZD5847 belongs to the oxazolidinone class of compounds, which function as protein synthesis inhibitors and were first discovered in the mid- 1980s.[3] Linezolid was the first compound of the oxazolidinone class to be approved for marketing and is most commonly used to treat drug-resistant TB.[4] However, the use of linezolid has been limited by toxicity concerns, particularly haematological effects after periods of treatment over 14 days.

AZD5847 (previously referred to as AZD2563, generic name posizolid) is a modified analogue of the linezolid compound. AZD5847 was originally designed for treatment of gram-positive infections but was subsequently repurposed as an anti-TB agent.[4] Like linezolid, AZD5847 has a bactericidal effect against mycobacterium TB in macrophages as well as in murine models of acute and chronic TB infection.

Chemical names for AZD5847 include:

- (5R)-3-[4-[1-[(2S)-2,3-dihydroxypropanoyl]-3,6-dihydro-2H-pyridin-4-yl]-3,5- difluoro-phenyl]-5-(isoxazol-3-yloxymethyl)oxazolidin-2-one;
- (5R)-3-[4-[1-[(2S)-2,3-Dihydroxy-1-oxopropyl]-1,2,3,6-tetrahydro-4-pyridinyl]-3,5-difluorophenyl]-5-[(3-isoxazolyloxy)methyl]-2-oxazolidinone; and
- (5*R*)-3-(4-{1-[(2*S*)-2,3-dihydroxypropanoyl]-1,2,3,6-tetrahydro-4-pyridyl}-3,5-difluorophenyl)-5-(1,2-oxazol-3-yloxymethyl)-1,3-oxazolidin-2-one.

The structure of AZD5847 is shown in figure 1.

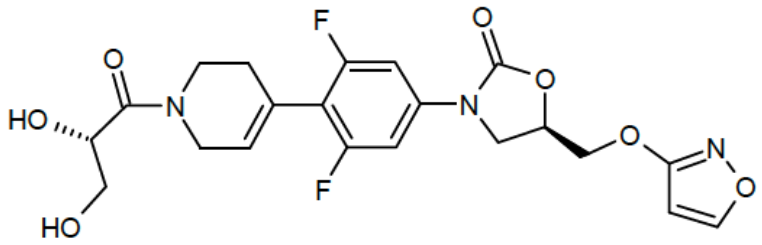

Figure 1. Structure of AZD5847

Phase I trials were completed recently. The results revealed that oral administration of AZD5847 up to 800 mg twice daily for 14 days was satisfactorily tolerated in healthy volunteers. While bioavailability decreases with increased dosing, this effect may be largely compensated for if the dose is taken within two hours of meals.[5]

AZD5847 is currently in Phase IIa clinical trials to assess the early bacterial activity from 0 to 14 days, including in patients with HIV coinfection.[6] Trials are being conducted in South Africa with the support of the National Institute of Allergy and Infectious Diseases.[7]

3 Marriner AG et al. The medicinal chemistry of tuberculosis chemotherapy. Topical Medical Chemistry. 2011;7:47-124.
4 Kolyva AS, Karakousis PC. Old and new TB drugs: mechanisms of action and resistance. Chapter 9, in: Cardona P-C. Understanding tuberculosis—new approaches to fighting against drug resistance. Rijeka, Croatia: InTech; 2012 (Open Access publication; DOI 10.5772/2477).
5 Subramanian B et al. AZD 5847—phase I experience. Presentation at: Gordon Research Conference on Tuberculosis Drug Development, Lucca, Italy, 3-8 July 2011.
6 See: http://clinicaltrials.gov/ct2/show/NCT01516203 (accessed 2 January 2014).
7 AstraZeneca Annual Report and Form 20-F Information 2012. London: AstraZeneca; 2012.

3. AZD5847: THE PATENT LANDSCAPE

The patent landscape in Annex I of this report sets out the key patents and patent applications for AZD5847, including their geographical patent coverage, as of March 2013. While every effort has been made to obtain comprehensive and accurate information on the status and geographical scope of the patents covering AZD5847, 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.

The patent searches identified seven relevant patents. For ease of reference these seven patents have been identified as Patents 1–7 in Annex I. All the patents were filed and remain in the name of Zeneca Limited or AstraZeneca UK Limited.

Patent 1 covers various oxazolidinone derivative compounds, including the base compound AZD5847, their process of preparation and pharmaceutical compositions. 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. On the basis of the information available, it appears that this patent has been refused or withdrawn in a number of countries or regions. These include Brazil, China, India and the USA, as well as Europe. This suggests that the equivalent patent application in other countries may also have been withdrawn or abandoned. Further checks would be necessary to confirm this.

Patent 2 covers chemical processes and intermediates relating to AZD5847. 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. On the basis of information available, it appears that this patent has been refused or withdrawn in a number of countries or regions. These include Brazil, China and India, as well as Europe. This suggests that the equivalent patent application in other countries may also have been withdrawn or abandoned. Further checks would be necessary to confirm this.

Patent 3 relates to a method for preparing AZD5847 and a hydrate salt thereof. The international patent application has been withdrawn and, therefore, has not entered the national phase stages of the countries designated.

Patent 4 relates to a process of phosphorylation for preparing AZD5847. The international patent application has been withdrawn and, therefore, has not entered the national phase stages of the countries designated.

Patent 5 relates to processes for intermediate compounds to prepare AZD5847. The international patent application has been withdrawn and, therefore, has not entered the national phase stages of the countries designated.

Patent 6 relates to a purification process for preparing AZD5847. The international patent application has been withdrawn and, therefore, has not entered the national phase stages of the countries designated.

Patent 7 covers the use of AZD5847 and a pharmaceutically acceptable salt to treat mycobacterium tuberculosis. 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. This could be because the international application has yet to enter the national phase and be published in designated countries. For example, despite searches conducted in the Indian Patent Office database, the application does not appear although India was designated in the international application. However, countries that may be of interest and where the patent application has entered the national phase include China, Philippines, Ukraine and Viet Nam, as well as the Eurasian Patent Office. Further checks are required to determine the current status of the applications for Philippines, Ukraine, Viet Nam and the Eurasian Patent Office.

Thus it is notable from the landscape that there is no protection for the base compound (Patent 1) in a number of key countries. This means that the base compound is open for use and formulation by other competitors. However, Patent 7, if granted, could potentially block competitors unless they can find an alternative salt form which is bioequivalent.

4. CONCLUSION

As this analysis shows, the base compound patent for AZD5847 does not appear to have been granted in many of the countries for which data have been obtained. Currently there are pending applications for a salt form of AZD5847 in various countries according to data available. However, as the base compound does not seem to be patented, even if the latter patent were granted, competitors might be able to use a different salt form.

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.[8] 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, given that AZD5847 is still in Phase II trials, it is too early to know what AstraZeneca's policy will be for making the drug accessible should it obtain marketing approval.

8 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.

ANNEX I: AZD5847 PATENT LANDSCAPE

	Patent 1	Patent 2	Patent 7
	Oxazolidinone derivatives, process for their preparation and pharmaceutical compositions containing them ***(This patent covers the base compound AZD5847 and the process for preparing the same)***	**Chemical processes and intermediates** ***(This patent covers processes and intermediates relating to AZD5847)***	**Compound for the treatment of tuberculosis** ***(This patent covers the use of AZD5847 and a pharmaceutically acceptable salt to treat mycobacterium tuberculosis)***
Applicant	**Zeneca Limited**	**AstraZeneca UK Limited**	**AstraZeneca UK Limited**
International Patent Publication No.	**WO 1999/64417**	**WO 2001/40236**	**WO 2010/106355**
Expected expiry (if granted and not subject to patent term extensions)	**2 June 2019**	**27 November 2020**	**15 March 2030**
	PATENT STATUS		
Argentina	Final status not available Pub No. 018452 App No. 1999102657	Application suspended Pub No. 026700	Pending Pub No. 075861 App No. 2010100833
Australia	Granted Patent No. 753998 Pub/App No. 19990041571	Granted Patent No. 762241 App No. 20010017156	Pending Pub/App No. 2010224619
		Final status not available Pub No. 1715601 App No. 20010017156	
Bulgaria	Final status not available Pub No. 105001 App No. 2000010500	Final status not available Pub No. 106728 App No. 20020106728	NA
Brazil	Application abandoned for non-payment of renewal fee Pub/App No. PI9910971	Application refused Pub/App No.PI0016087	NA
Canada	Application abandoned/ withdrawn Pub No. 2333332 App No. 19992333332	Application abandoned Pub No. 2395052 App No. 20002395052	Pending Pub No.2755209 App No. 20102755209
China	Application withdrawn Pub No. 1311787 App No. 1999809352	Application withdrawn Pub No. 1433421	Pending Pub No. 102355901 App No. 20108011955
Colombia	NA	Application withdrawn Pub No. 5271712 App No. 20000090190	NA

	Patent 1	Patent 2	Patent 7
Czech Republic	Application withdrawn Pub No. PV2000-4498	Application refused Pub No. PV2002-1912	NA
Estonia	Final status not available Pub/App No. 200000707	Final status not available Pub/App No. 200200282	NA
Eurasian Patent Office	NA	NA	Pending Pub/App No. 201101328
European Patent Office	Application refused Pub No. 1082323 App No. 99925188	Application withdrawn Pub No. 1237895 App No. 00979764.8	Pending Pub No. 2408452 App No. 10710617.1
Hungary	Final status not available Pub No. 0103082 App No. 20010003082	Final status not available Pub No. 0204052 App No. 20020004052	NA
Iceland	Final status not available Pub No. 5747 App No. 20000005747	Final status not available Pub No. 6401 App No. 20020006401	NA
India	Application withdrawn Pub/App No. IN/PCT/2000/00658/MUM	Application withdrawn Pub/App No. IN/PCT/2002/00641/MUM	NA
Indonesia	Final status not available Pub No. 0103082 App No. 20010003082	NA	NA
Israel	Final status not available Pub/App No. 140084	Final status not available Pub/App No. 149641	Pending Pub/App No. 214715
Japan	Final status not available Pub No. 2002517498 App No. 20000553426	Final status not available Pub No. 2003515539 App No. 20010540991	Pending Pub No. 2012520864 App No. 20120500313
Mexico	Final status not available Pub/App No. 00011536	Final status not available Pub/App No. 02005396	Pending Pub/App No. 2011009263
New Zealand	Granted Patent No. 508174 Pub/App No. 508174	Final status not available Pub No. 519083	Pending Pub/App No. 595724
Philippines	NA	NA	Pending Pub/App No. 12011501834
Poland	Application refused Pub/App No. 345162	Final status not available Pub/App No. 364762	NA
Republic of Korea	Application withdrawn App No. 1020007013819	Application withdrawn App No. 1020027007072	Pending Pub No. 20110127219 App No. 20117021496
Russia	NA	Final status not available App No. 20022002117647	NA
Singapore	Final status not available App No. 200067926	Final status not available App No. 2002030443	Pending Pub No. 173770 App No. 20110005984
Slovakia	Final status not available Pub/App No. 18362000	Final status not available Pub/App No. 7862002	NA

	Patent 1	Patent 2	Patent 7
South Africa	Final status not available Pub/App No. 200006694	Final status not available Pub/App No. 200203876	NA
Taiwan, China	NA	NA	Pending Pub No. 201036609 App No. 20100107448
Turkey	Final status not available Pub/App No. 200003595	NA	NA
Ukraine	NA	NA	Pending Pub/App No. 201111971
Uruguay	NA	NA	Pending Pub No. 32493 App No. 20100032493
USA	Expired – Non-payment of renewal fees Patent No. 6617339	NA	Pending Pub No. 20120035219 App No. 13/256658
	Application abandoned Pub No. 20030144263 App No. 10/340526		
Viet Nam	NA	NA	Pending Pub No. 28580 App No. 20112270

NA – Data not available or international application had not entered the national phase and was not published at the time the patent searches were conducted (March 2013).

Eurasia Patent Office covers: Armenia, Azerbaijan, Belarus, Kazakhstan, Kyrgyzstan, Republic of Moldova, Russian Federation, Tajikistan and Turkmenistan.

	Patent 3	Patent 4	Patent 5	Patent 6
	Chemical processes and intermediates *(This patent covers a method for preparing AZD5847 and a hydrate salt thereof)*	**Process for phosphorylation** *(This patent covers a method/process for preparing AZD5847)*	**Purification process and intermediates** *(This patent covers processes for intermediates relating to AZD5847)*	**Purification process** *(This patent covers processes for preparing AZD5847)*
Applicant	**AstraZeneca UK Limited**	**AstraZeneca UK Limited**	**AstraZeneca UK Limited**	**AstraZeneca UK Limited**
International Patent Publication No.	**WO 2002/096890**	**WO 2002/096916**	**WO 2002/096917**	**WO 2002/096918**
Expected expiry (if granted and not subject to patent term extensions)	**28 May 2022**	**28 May 2022**	**28 May 2022**	**28 May 2002**
PATENT STATUS				
These applications have been withdrawn.				