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A Review of the Sutezolid (PNU-100480) 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 Pfizer's investigational compound sutezolid (previously known as PNU-100480). Sutezolid has been identified as a possible new treatment for drug-susceptible TB (DS-TB) and MDR-TB.

Given the potential of sutezolid, 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

Sutezolid 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 treatment of TB. It is most commonly used to treat drug-resistant TB.[4] However, linezolid's use has been limited by toxicity concerns, particularly haematological effects after periods of treatment over 14 days.

The compound structure of sutezolid (see Figure 1) is a modified analogue of the linezolid compound, but has been shown to have more potent activity. Sutezolid was one of the earlier oxazolidinone antibiotics synthesized that exhibited increased antimycobacterial activity compared with linezolid; the potential of sutezolid as an anti-TB agent being recognized around 1994. However, it was pursued as an option for treating DS-TB and MDR-TB only more recently. Recent studies using the mouse model have shown that the addition of sutezolid to the standard first-line regimen of rifampicin, isoniazid and pyrazinamide can shorten the duration of treatment necessary to prevent relapse, thus suggesting that sutezolid may have sterilizing activity against DS-TB and MDR-TB.[5]

Chemical names for sutezolid include:

- acetamide, *N*-[[(5*S*)-3-[3-fluoro-4-(4-thiomorpholinyl)phenyl]-2-oxo-5-oxazolidinyl] methyl]- ; and
- *N*-({(5*S*)-3-[3-fluoro-4-(thiomorpholin-4-yl)phenyl]-2-oxooxazolidin-5-yl}methyl) acetamide.

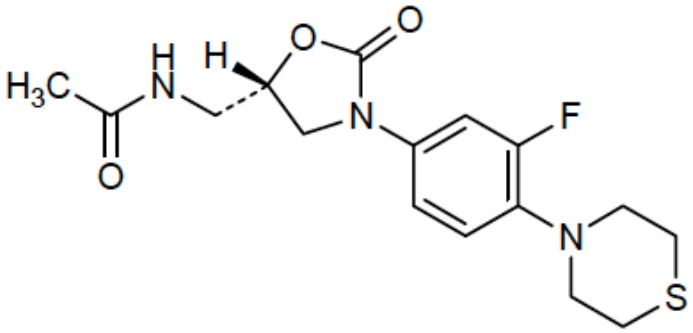

Figure 1. Structure of sutezolid

Phase I trials revealed that sutezolid is safe and well tolerated at all tested doses and that it exihibits synergy with pyrazinamide. It is expected that resistance mechanisms will be similar to those of linezolid.[4]

Several Phase IIa clinical trials have been conducted to assess sutezolid's early bactericidal and whole-blood activity in newly diagnosed treatment-sensitive patients.[6]

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 Williams KN et al. Addition of PNU-100480 to first-line drugs shortens the time needed to cure murine tuberculosis. American Journal of Respiratory and Critical Care Medicine. 180(4):371-376.
6 See: http://clinicaltrials.gov/ct2/show/NCT01225640 (accessed 2 January 2014).

3. SUTEZOLID: THE PATENT LANDSCAPE

The patent landscape in Annex I of this report sets out the key patents and patent applications for sutezolid, including their geographical patent coverage, as of April 2013. While every effort has been made to obtain comprehensive and accurate information on the status and geographical scope of the patents covering sutezolid, 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 two relevant patents. For ease of reference these two patents have been identified as Patent 1 and patent 2 in Annex I. These patents were filed in the name of The Upjohn Company (Patent 1) and Pfizer Inc and Johns Hopkins University (Patent 2).

Patent 1 covers the base compound sutezolid and its use as an antibacterial, including use against mycobacterium tuberculosis. 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 Brazil and China. No corresponding application or granted patent was found in India. The international patent application has entered the national phase in Philippines and South Africa but further checks are required to determine the current status of these applications.

Given that Pfizer reportedly started pursuing development of sutezolid some time after the patent application for the base compound was filed, it is possible that that protection was not pursued in many countries. This would, however, need to be confirmed through further searches in the territories of interest.

Patent 2 covers a combination therapy comprising sutezolid and two additional compounds used to treat TB. The additional compounds listed include PA 824, delamanid, bedaquiline, SQ-109, rifampicin and moxifloxacin. Given that the international application for Patent 2 has been filed relatively recently, it is likely to have been applied for in a higher number of countries where there is a potential market for the product. However, as the application is recent, there is limited information regarding the countries where it has entered the national phase. For example, searches do not show the international application as having yet been published or having entered the national phase in Brazil or India. However, key countries where the patent has entered the national phase and is pending are China, Russia and South Africa. Further checks would be necessary to establish the current status in Russia and South Africa.

It should be noted that the scope of Patent 2 is limited only to the use of sutezolid in combination with other compounds to treat TB. Therefore Patent 2 would not prevent competitors using, formulating and selling medicines containing sutezolid alone or in combination with other non-patented TB treatments in countries where Patent 1 was not applied for.

4. CONCLUSION

As this analysis shows, the base compound patent for sutezolid does not appear to have been filed in India. As such, generic companies in India would be able to use and formulate sutezolid, either alone or in combination with other non-patented TB medicines. Whether other countries would subsequently be able to import and use those medicines would depend on whether the relevant patents have been filed and granted at the national level in the importing countries.

Determining the patent situation is a useful starting point for understanding possible access issues, since patents can bar competitors from manufacturing, selling, importing or exporting a product.[7] 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 sutezolid is still in Phase II trials, it is too early to know what the patent-holders' policy will be for making sutezolid accessible should it obtain marketing approval.

7 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: PNU-100480 (SUTEZOLID) PATENT LANDSCAPE

	Patent 1	**Patent 2**
	Substituted oxazine and thiazine oxazolidinone antimicrobials ***(This patent claims the base compound sutezolid and its use as an antibacterial, including against mycobacterium tuberculosis)***	**Combination therapy for therapy for tuberculosis** ***(This patent claims the combination of PNU-100480 (sutezolid) with two additional compounds used to treat tuberculosis, including the investigational compounds PA 824, SQ-109, delamanid [OPC-67683] and bedaquiline [TMC207])***
Applicant	**The Upjohn Company**	**Pfizer Inc and Johns Hopkins University**
International Patent Publication No.	**WO 1995/07271**	**WO 2010/026526**
Expected expiry (if granted and not subject to patent term extensions)	**15 August 2014**	**30 August 2029**
	PATENT STATUS	
Australia	Granted Patent No. 687866 App/Pub No. 19940075570	Pending App/Pub No. 20090288820
Brazil	Granted Patent No. 1101033-9 App/Pub No. 1101033-9	NA
Canada	Granted Patent No. 2168560 Pub/App No. 19942168560	Pending Pub No. 2735229 App No. 20092735229
China	Granted Patent No. 1057087 Pub No. 1130379 App No. 19941093313	Pending Pub No. 102143748 App No. 20098134310
China, Hong Kong SAR	NA	Pending Pub No. 1155971 App No. 2011110319
European Patent Office	Granted Patent No. 0717738 Pub No. 0717738 App No. 94925765	Pending Pub No. 2340022 App No. 09787058
India	No patent found	NA
Israel	Granted Patent No. 110802 Pub/App No. 19940110802	Pending Pub/App No. 211293

	Patent 1	Patent 2
Japan	Granted Patent No. 3176630 Pub No. 09502436 App No. 19950508665	Pending Pub No. 2012502017 App No. 20110525657
Latvia	Granted Patent Number 12605 Pub No. 12605 App No. 20000000142	NA
Mexico	Granted Patent No. 197282 Pub/App No. 19946909	Pending Pub/App No. 2011002348
New Zealand	Granted Patent No. 271805 Pub/App No. 271805	Pending Pub/App No. 591169
Philippines	Final status not available Pub No. 31634 App No. 19940048830	NA
Republic of Korea	Granted Patent No. 301269 Pub/App No. 1996701191	Pending Pub No. 20110063518 App No. 20117007672
Russia	NA	Pending Pub/App No. 2011108026
Slovenia	Granted Patent No. 717738 Pub/App No. 19940030287	NA
South Africa	Final status not available Pub/App No. 9405894	Pending Pub/App No. 201101742
Taiwan, China	Final status not available Pub No. 293817 App No. 1994107479	NA
USA	Granted Patent No. 5688792 App No. 617/877	Pending Pub No. 20110190199 App No. 13/061233
USA	Granted Patent No. 5880118 App No. 886965	

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