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**A Review of the PA-824
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 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 that is currently in the pipeline and generating interest is the TB Alliance's investigational compound PA-824. PA-824 has been identified as a possible new treatment for drug-susceptible (DS) and MDR-TB.

Given the potential of PA-824, 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

Like delamanid, PA-824 belongs to the nitroimidazoles class of compounds and is a derivative of compound CGI-17341 whose anti-TB activity was reported as early as 1993.³ PA-824 was discovered by Patho-Genesis Corporation, which was subsequently acquired by Chiron Corporation. Novartis AG acquired Chiron Corporation in 2006.

PA-824 is a pro-drug, which requires reductive activation of an aromatic nitro group before it becomes effective against TB bacteria.⁴ Pre-clinical studies have demonstrated that PA-824 has potent bactericidal and sterilizing effects against DS-TB and MDR-TB. PA-824 has also been shown to be active against latent TB bacteria.⁴

Chemical names for PA-824 are:

- (6S)-2-nitro-6-{[4-(trifluoromethoxy)benzyl]oxy}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine; and
- (3S)-8-nitro-3-[[4-(trifluoromethoxy)phenyl]methoxy]-5-oxa-1,7-diazabicyclo[4.3.0]nona-6,8-diene.

The structure of PA-824 is shown in Figure 1.

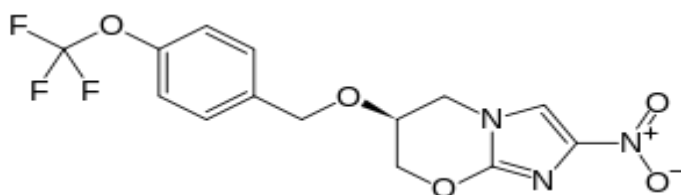


Figure 1. Structure of PA-824

The TB Alliance is leading the development of PA-824, having gained global exclusive rights to this compound and to related ones for the treatment of TB following an agreement with Chiron in 2002. It is understood that the agreement with Chiron ensured that PA-824 would be made available royalty-free in endemic countries.⁴

According to a statement by the TB Alliance, in 2007 the United States Food and Drug Administration (FDA) and the European Union approved a request for orphan drug designation of PA-824.⁵ The designation as an orphan drug confers a number of benefits for the development of PA-824, including a waiver of the nearly US\$ 1 million fee usually paid on submission of a new drug application. The FDA has also granted PA-824 fast-track designation, which is intended to expedite the application and review process for products that have the potential to address serious or life-threatening conditions.⁵

PA-824 is currently undergoing Phase II trials.⁶ The development of PA-824 was put on hold by the FDA following reports that it caused cataracts in monkeys. However, Phase I trials found no evidence of this side-effect. Phase II trials in South Africa revealed bactericidal activity similar to that demonstrated by the standard first-line combination.

3 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.

4 Leavens J. PA-824. *TB Online*. New York, NY: Global Tuberculosis Community Advisory Board; 16 September 2011 (<http://www.tbonline.info/posts/2011/9/16/pa-824/>, accessed 2 January 2014).

5 TB Alliance advances two drugs in clinical trials on path to faster, better tuberculosis treatments. New York, NY: TB Alliance; 11 August 2007 (<http://new.tballiance.org/newscenter/view-brief.php?id=726>, accessed 2 January 2014).

6 Stop TB Partnership Working Group on New TB Drugs. Drug pipeline: PA-824. Geneva: Stop TB Partnership; 2013 (<http://www.newtbdrugs.org/project.php?id=25>, accessed 2 January 2014).

3. PA-824: THE PATENT LANDSCAPE

The patent landscape in Annex I of this report sets out the key patents and patent applications for PA-824, 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 PA-824, in many countries patent information is not readily available to the public or is 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 one relevant patent. For ease of reference this patent has been identified as Patent 1 in Annex I. The patent was filed in the name of PathoGenesis Corporation (now owned by Novartis AG after its acquisition of Chiron Corporation).

Patent 1 covers various nitroimidazole antibacterial compounds (including PA-824), their methods of use and 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. This could be due to the international application designating only a limited number of countries or regions, some of which may not have been pursued. Further searches would be necessary to confirm the status of the international application in the designated territories of the African Regional Intellectual Property Office (ARIPO) and Eurasian Patent Office. Searches conducted in India did not reveal a corresponding patent application.

4. FACTORS AFFECTING ACCESS TO PA-824

As noted in Section 2, according to information released by the TB Alliance, Chiron Corporation granted global exclusive rights to PA-824 and related compounds for the treatment of TB. It is understood that the agreement with Chiron ensures that PA-824 will be made available royalty-free in endemic countries.

If the information available is accurate, it would appear that the TB Alliance would have no restrictions as to where PA-824 can be marketed, if and when approved. This could mean that the TB Alliance will be able to make PA-824 available in both low-income and middle-income countries. At present there is little information on how the TB Alliance will manufacture PA-824. One possibility is that it may choose to partner with generic firms in India to manufacture the product at low cost.

Aside from the TB Alliance having global exclusive rights to PA-824, it is noticeable that the patent coverage for the base compound does not seem to be extensive. However, further searches would be necessary to confirm whether Patent 1 has entered the national phase and/or has been granted in any of the designated states of ARIPO and the Eurasian Patent Office, as designated in the international application. Given that Patent 1 does not appear to have been filed in India, generic companies there would be able to produce PA-824. However, whether there will be generic competition will depend on a number of other factors, including demand for PA-824 and the TB Alliance's access and licensing strategies.

In determining the patent landscape for PA-824 and any potential impact on access, it is also relevant that Patent 1 is expected to expire in 2016. Given that PA-824 is still in Phase II clinical trials, it may receive marketing approvals after the expiry of the base compound patent.

5. CONCLUSION

On the basis of publicly available information, the TB Alliance has royalty-free global exclusive rights to market PA-824 in all endemic countries. Therefore it would appear that the patent covering the base compound should not be an obstacle to making the product accessible at affordable prices, should it receive marketing approval.

At the time of writing there was little public information on the TB Alliance's policy on pricing of and access to PA-824.

It is worth noting that, irrespective of the TB Alliance's access to the patent rights for PA-824, there is the possibility that generic manufacturers in India could produce the product without restriction as no application for the base compound was filed there. It is also possible that the patent for the base compound will expire before any marketing approval for PA-824 is granted.

ANNEX I: PA-824 PATENT LANDSCAPE

	Patent 1¹ Nitroimidazole antibacterial compounds and methods of use thereof <i>(This patent claims the base compound PA-824 and its methods of use and composition)</i>
Applicant	Pathogenesis Corporation
International Patent Publication No.	WO 1997/01562
Expected expiry (if granted and not subject to patent term extensions)	24 June 2016
	PATENT STATUS
Australia	Granted Patent No. 706448 Pub/App No. 6395469
Canada	Granted Patent No. 2225822 Pub/App No. 2225822
European Patent Office	Granted Patent No. 0866793 Pub No. 0866793 App No. 96923477
India	No patent found
Japan	Granted Patent No. 4621819 Pub No. 11508270 App No. 19970504536
USA	Granted Patent No. 5668127 App No. 496850
USA	Granted Patent No. 6087358 App No. 08/924559

¹ Patent searches were conducted in April 2013.