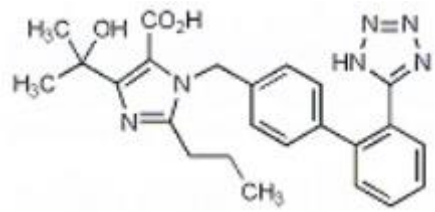
Drug In Focus: Olmesartan

April 2016

Daiichi Sankyo's Olmesartan franchise (Benicar®, Benicar HCT®, Azor® and Tribenzor®) is set to lose patent protection in Oct 2016 due to expiry of one of its strongest patents 'US5616599'. This opens up a market worth ~US$2.3 billion to generic competition. Daiichi's life cycle management strategy to combine Olmesartan with other antihypertensive drugs will protect some of the revenues, but generics of Benicar® and Benicar HCT® are expected to erode much of the revenue share.

General information

Developed by Sankyo (now Daiichi Sankyo), Olmesartan is marketed as Benicar® for the treatment of hypertension. This is also available in combination with other antihypertensive drugs. According to IMS Health, Daiichi Sankyo 2015 sales in the US market for all their Olmesartan products generated US$2,316 million. Olmesartan was first authorised by the FDA in 2002 in the form of a medoximil prodrug as tablets in 5, 20, 40 mg strengths. In the US, Olmesartan is authorised in a fixed dose combination with Hydrochlorothiazide as Benicar HCT®, with Amlodipine Besylate as Azor® and with Amlodipine Besylate and Hydrochlorothiazide as Tribenzor®.



Chemical Name:	4-(2-hydroxypropan-2-yl)-2-propyl-1-{[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl}-1H-imidazole-5-carboxylic acid
Formulation:	Oral tablets
Combinations:	Amlodipine, Hydrochlorothiazide, Olmesartan Amlodipine, Olmesartan Hydrochlorothiazide, Olmesartan

Figure 1: Olmesartan chemical structure, formulation and combination details

INN Constraint Comment

Currently, Benicar® and Benicar HCT® are protected by key patent families with priorities JP2709891A (1991-02-21) and JP2000354327A (2000-11-21), (Fig 2) which are both owned by Daiichi. The US member, US5, 616, 599 ('599), of the family protects the molecule and its use in the treatment of hypertension, so is considered to constrain generic entry for all Olmesartan dosage forms until expiry. The patent protection on the '599 molecule patent is set to expire on 25 October, 2016 due to a six month paediatric extension to a 755 day Hatch-Waxman patent term extension, Benicar® and Benicar HCT® will no longer have market protection from generic entry from this date onwards.

Following data exclusivity expiry of Benicar® in 2007, the validity of the '599 patent was tested after Mylan filed an Abbreviated New Drug Applications (ANDA) with Paragraph IV certifications to manufacture generic Olmesartan medoxomil tablets. Consequently, Daiichi filed a patent infringement suit against Mylan, similar cases were also filed following Mylan's ANDA filings to manufacture generic Olmesartan medoxomil and Hydrochlorothiazide tablets and Olmesartan medoxomil and Amlodipine Besylate tablets. The proceedings were consolidated in the US District Court for the District of New Jersey. Mylan asserted that Claim 13 of the '599 patent disclosing the Olmesartan chemical name was invalid as obvious. In 2009, the Court found that Mylan failed to prove that '599 was obvious under 35 U.S.C § 103(a) and had infringed the patent. This case is now closed. With the US District Court ruling in favour of Daiichi, generic manufacturers could see the strength of the '599 patent and its ability to protect Olmesartan medoxomil as well as its combination products from generic entry.

The Orange Book listed patent US6, 878, 703 ('703) of family with priority JP2000354327A, protects the combination of Olmesartan and a diuretic, however this patent lapsed in 2009 due to Daiichi failing to pay maintenance fees and is no longer enforceable or considered to be a constraint for generic entry. In 2009, Daiichi requested it to be delisted from the Orange Book, however it still remains listed in the Orange Book because the FDA has not removed it.

Priority Number	Patent Scope	Patent Number	Key Patent Source	Patent Expiry	Extension Expiry
JP2709891A (1991-02-21)	Olmesartan molecule, its medoxomil ester and their use in the treatment of hypertension.	US5616599		2014-04-01	2016-04-25 2016-10-25 (PED)
JP2000354327A (2000-11-21)	Combination of Olmesartan and a diuretic, preferably Hydrochlorothiazide, and their use in the treatment of hypertension.	US6878703		Lapsed	

Figure 2: US Patents protecting OLMESARTAN and HYDROCHLOROTHIAZIDE, OLMESARTAN
Key Patent Source: - FDA Orange Book Listed; - Patent Term extensions applied/granted; - Litigation Case

Following the patent expiry of Amlodipine molecule in 2007, Daiichi joined other competitor products in the antihypertensive products to combine the calcium channel blocker, Amlodipine and an angiotensin II receptor blocker. Daiichi received FDA approval for Azor® and Tribenzor® in 2007 and 2010 respectively. Three years of data exclusivity available in the US for new combinations has expired for both products and therefore there is no longer a constraint to generic entry. As discussed above, the patents in family JP2709891A protect Olmesartan and its use in the treatment of hypertension, hence it is considered constraining for these combination products. Ark Patent Intelligence has also identified a series of US patent applications that could potentially constrain generic entry for the combination products if issued by the USPTO. The patents seek to

protect the combination of Olmesartan medoxomil and Amlodipine and its use in the treatment of hypertension. The claims of the patent were rejected due to lack of novelty, but this has been appealed at the USPTO. Competing products such as Novartis' Exforge® (Valsartan, Amlodipine) and Exforge HCT® (Valsartan, Amlodipine, Hydrochlorothiazide) have already experienced generic competition in the US. Despite Orange Book listed patents protecting both of Novartis' products, generic manufacturers have filed and been granted ANDAs with Paragraph IV certification to the Orange Book listed patents but no infringement action was taken. It is important to monitor these patent applications for the Olmesartan and Amlodipine combinations and subsequent listings in Orange Book, although they may not affect the approval of an existing ANDA application, they may later cause patent infringement proceedings.

According to IMS Health, Benicar® and Benicar HCT® attributed $1,786 million of the $2,316 million of the US revenue for 2015, Azor® contributed $329 million and Tribenzor® $202 million. While there is an attempt by Daiichi to retain a proportion of the Olmesartan market by marketing new combination products with longer periods of market exclusivity, Benicar® and Benicar HCT® remain to be the most desirable products for generic investment based on the revenue contributed to Olmesartan products. This is also reflected in the number of ANDAs that have been filed by generic manufacturers to the FDA (Fig 3).

Active Ingredient	Product name	ANDA filings
Olmesartan medoxomil	Benicar®	6
Olmesartan medoxomil; Hydrochlorothiazide	Benicar HCT®	3
Olmesartan medoxomil; Amlodipine Besylate	Azor®	4
Olmesartan medoxomil; Amlodipine Besylate; Hydrochlorothiazide	Tribenzor®	0

Figure 3: ANDA filings for Olmesartan and its combinations

For generic manufacturers, being 'first to market' is very important in order to gain a significant market share for the generic product. Mylan has entitlement to the 180-day exclusivity for Benicar® and Benicar HCT® equivalents for being the first-to-file an ANDA with a Paragraph IV. However, this could potentially be eroded due to the actions taken by Apotex which could trigger forfeiture of Mylan's entitlement and allow other generic competitors on to the market earlier.

One instance where forfeiture may arise is if the subsequent filer has obtained a final and non-appealable judgement of invalidity or non-infringement of the patents(s), (with the exception of a petition for writ of certiorari to the Supreme Court) and them having obtained a tentative ANDA. Once the Court has issued its final and non-appealable decision, the first-filer must market its products within 75-days of the Court's decision. If the product is not marketed within the 75-day period and the 30-month period after the ANDA filing date has not yet lapsed, the first-filer's market exclusivity period may be forfeited.

In 2012, Apotex filed an ANDA with a Paragraph IV certification to the disclaimed, but Orange Book listed patent '703 for Benicar® and Benicar HCT®, and filed a suit seeking for declaratory judgement of invalidity or

non-infringement of the patent in the US District Court of the Northern District of Illinois (Apotex's case). In March 2016, following appeals to US Court of Appeals for the Federal Circuit to allow Apotex's case to be heard, the District Court for the Northern District of Illinois handed down its final judgement of non-infringement for '703. The decision is subject to a potential appeal. Apotex, has not yet gained a tentative approval for Benicar® and Benicar HCT® and therefore the 75-day period will not be triggered until they do or any appeal and a non-infringement decision becomes non-appealable. Even if Apotex is unable to gain a tentative ANDA, a non-appealable decision of non-infringement of the patent could trigger the 75-day period because of other subsequent filers, Sandoz and Teva (Fig. 3). However, case law is silent on whether the combination of subsequent filers who have gained tentative ANDA approvals, along with a non-appealable decision in the Apotex case could potentially trigger the forfeiture provisions. It may be up to the FDA to interpret the failure to market forfeiture provision of the Medicare Prescription Drug Modernization and Improvement Act (2003) in relation to the 180-day exclusivity. The FDA will not approve a final ANDA until after the expiry of the molecule patent in October 2016.

Summary

Daiichi's life cycle management strategy to market Olmesartan along with other antihypertensive drugs as new products has been successful as Azor® and Tribenzor® made a combined total of $530 million for 2015 in the US market. It is clear that the '599 patent is the major blocker for generic versions of Olmesartan, which is highlighted by the litigation cases in which it has been successfully upheld as valid and infringed by generic manufacturers. Upon expiry of the '599 patent, Daiichi will be able to protect some of the revenue through these combination products, but the company will suffer a significant revenue loss for Benicar® and Benicar HCT® once the '599 patent expires due to generic erosion. It is expected that once '599 patent expires generic versions of Olmesartan will be ready to enter the US market.

The landscape of the multi-billion dollar US cardiovascular market is set to face serious competition from an influx of generic manufacturers. In 2016, along with Benicar® other blockbuster drugs in cardiovascular segment (Crestor® and Zetia®) will also lose patent protection; making this a highly lucrative area for generic pharmaceutical manufacturers.

This article looks at the patent landscape for Olmesartan and its combinations in the US market using ARK Patent Intelligence data assets. For more information concerning patent landscape in additional markets or to find out more about Ark Patent Intelligence and how it can assist your generic drug development, please visit www.arkpatentintelligence.com

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