Ezetimibe attracts additional interest

In light of the vast profits on offer, it is hardly surprising that the fight to be the first paragraph IV filer in the US is fierce. On the first day possible, several firms file paragraph IV certifications, claiming that patents protecting many brands are invalid, unenforceable or not infringed. However, for other drugs, ANDA filings occur less frequently and more sporadically, giving generic challengers greater time to make measured decisions on whether and how to compete.

With around US$1.4 billion in annual US brand sales, the Zetia (ezetimibe) cholesterol-lowering tablets marketed by Merck/Schering-Plough certainly appear to offer rich rewards to any firm that can successfully overcome patents protecting the blockbuster brand. Indeed, as Thomson Reuters observes, two of the industry's top three players – Mylan and Teva – have recently submitted ANDAs containing paragraph IV certifications to Zetia patents, even though Glenmark first moved against the patents four years ago and appears to have secured a head start when it launches of 180-day generic exclusivity.

The US Food and Drug Administration (FDA) says it received the first paragraph IV certification relating to Zetia on 25 October 2006, the first day on which the agency could accept ANDA filings due to new chemical entity (NCE) exclusivity. "Because Glenmark was the only company sued for infringement at that time, we assume it was the sole first filer," Thomson Reuters comments.

Schering-Plough alleged in a New Jersey district court that Glenmark had infringed reissued US patent RE37,721. This is a key patent that covers Zetia's active ingredient, delivery form and use to control plasma cholesterol, expiring on 25 April 2017. The Indian generics firm offered several defences, including invalidity as a result of double-patenting and unenforceability due to inequitable conduct (**Generics *bulletin***, 6 April 2007, page 14).

In April this year, the court granted Glenmark summary judgement that claims 3-10 of the '721 patent were invalid because they had been improperly reissued. However, before a full trial on invalidity due to double-patenting could start on 12 May, the two parties reached a settlement and asked the court to vacate its summary judgement. Under the disclosed terms of the settlement, Glenmark – or rather its US partner Par – can launch ezetimibe from 12 December 2016, or earlier under certain circumstances (**Generics *bulletin***, 28 May 2010, page 14).

"Clearly, the summary judgement of invalidity due to improper reissue – even though it has been vacated – showed some significant weakness in the patent," Thomson Reuters asserts. Before the patent holders could submit another reissue application in June this year, Mylan filed an ANDA for ezetimibe and was promptly sued over the '721 patent as well as another patent which the originator had not enforced against Glenmark – US patent 5,846,966 which expires on 21 March 2014. Teva followed suit and was similarly sued.

"There appears to be little to lose for Mylan and Teva at this point," Thomson Reuters believes. If their patent challenges succeed, they are likely to bring forward the time when Par launches with 180-day exclusivity through Glenmark's settlement, thereby accelerating their own market entry. And if they lose, the timing of Zetia's patent expiries means they are still likely to come to market six months after Par, justifying their limited litigation costs given the size of the original. "The visible presence of such major players," Thomson Reuters speculates, "may encourage potential rivals to look elsewhere."

KEY DETAILS

Brand:	Zetia
Active ingredient:	ezetimibe
Delivery form:	10mg tablets
Brand owner:	Merck&Co/Schering-Plough
Annual US brand sales:	US$1.4 billion*
First paragraph IV filing accepted by FDA:	25 October 2006
Known paragraph IV filers:	Glenmark; Mylan and Teva
Patents at issue – expiry dates:	5,846,966 – 21 March 2014** RE37,721 – 25 April 2017**
District court location:	New Jersey
Litigation references:	Schering-Plough vs Glenmark 2:07-cv-01334 Schering-Plough vs Mylan 2:10-cv-03085 Schering-Plough vs Teva 2:10-cv-04473
Other FDA Orange Book patents with expiry dates:	7,030,106 – 25 July 2022** 7,612,058 – 25 July 2022**

* IMS Health data cited by Glenmark
** including six months of paediatric exclusivity

Figure 1: Key details of paragraph IV challenges to Merck/Schering Plough's Zetia (ezetimibe) tablets in the US (Source – Thomson Reuters)

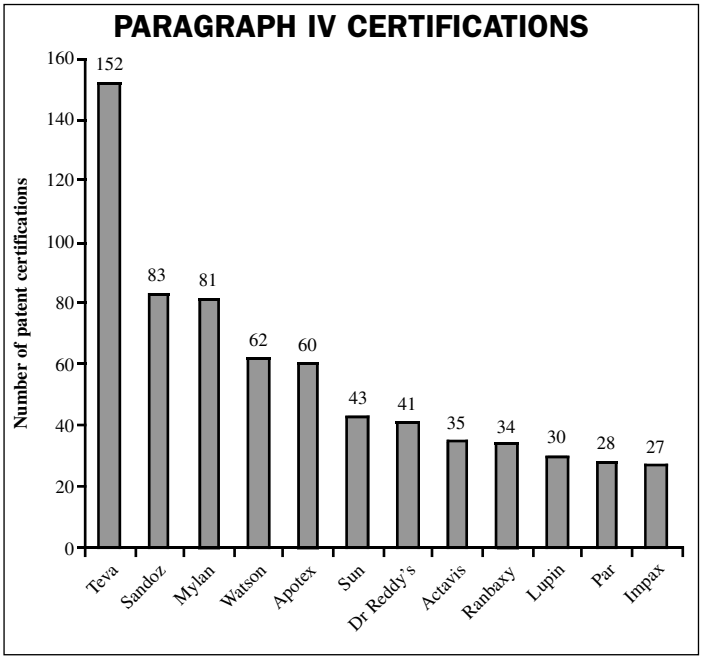

Figure 2: The number of cumulative US paragraph IV patent certifications on record for selected companies as of June 2010 (Source – Thomson Reuters)