Firms are awake to Silenor opportunity

One strategy that innovators have used to counter weak pipelines of novel drugs has been to develop new indications and formulations for older compounds. Recent paragraph IV challenges in the US – such as those to Shire's Intuniv (guanfacine) extended-release tablets (**Generics *bulletin***, 28 May 2010, page 20) – have shown one problem with this strategy, namely the lack of new chemical entity (NCE) exclusivity. This exclusivity precludes submissions of abbreviated new drug applications (ANDAs) that include paragraph IV certifications for four years from the date of the original drug's approval.

Somaxon Pharmaceutical's Silenor (doxepin hydrochloride) tablets are another dramatic example of how aggressively generics companies are targeting products and how the lack of NCE exclusivity can reduce the time between new drug application (NDA) approval and the submission of generic challenges.

Silenor tablets are a low-dose formulation of the tricyclic antidepressant doxepin that is indicated for sleep-maintenance insomnia. While they do not qualify for NCE protection, they are subject to a new-product exclusivity that bars ANDA approvals until March 17, 2013, three years from the date of approval for Somaxon's NDA.

However, as Thomson Reuters points out, even that period of protection is effectively reduced because although the US Food and Drug Administration (FDA) approved Silenor in March 2010, the insomnia treatment's commercial launch was delayed until September last year. On 7 September 2010, Somaxon announced the commercial availability of the product. Full-scale promotion and marketing – in partnership with Procter & Gamble – began on 20 September.

Although existing sales of doxepin hydrochloride products were quite modest – IMS Health reports US sales of US$14.2 million for the 12 months ended June 2010 – generics firms were clearly watching Silenor's progress and ready to act when the opportunity arose.

"The FDA reports the first submission of an ANDA containing a paragraph IV certification for a generic version of Silenor on 16 September 2010, just over a week after Somaxon announced the commercial availability of the product and four days before the start of promotion of the NDA product," Thomson Reuters highlighted.

Somaxon received paragraph IV notification letters from Actavis and Mylan on 3 November last year and filed suit against them in a Delaware district court on 15 December (see Figure 1). This action triggered 30-month stays on ANDA approval until early May 2013, less than two months after Silenor's new-product exclusivity ends. On 23 December, the originator received notice of Par's ANDA. "Presumably a suit against Par will be filed shortly," Thomson Reuters commented.

According to Somaxon, paragraph IV certifications were submitted by three ANDA filers to seven of the eight formulation or method-of-use patents listed against Silenor in the FDA's Orange Book. However, the suit against Actavis and Mylan alleges infringement only of US patent 6,211,229, which concerns the treatment of transient and short-term insomnia and expires on 17 February 2020. According to the Orange Book, six patents covering the drug product expire on 9 January 2015, while another patent covering the treatment of insomnia expires on 26 March 2013.

As Figure 2 shows, five-year NCE exclusivity for several significant brands – including an array of aliskiren-based products – ends in the first half of 2012. As the FDA is permitted under US law to accept ANDAs containing paragraph IV certifications one year before NCE exclusivity for the reference drug expires, generics firms have several targets at which to take aim over the next few months.

The FDA's decision to grant NCE exclusivity to Shire's Vyvanse (lisdexamfetamine) attention deficit hyperactivity disorder (ADHD) drug until February 2012 was recently upheld by the Court of Appeals for the District of Columbia. This followed a challenge by Actavis (**Generics *bulletin***, 26 March 2010, page 18). G

KEY DETAILS: SILENOR

Brand:	Silenor
Active ingredient:	doxepin hydrochloride
Delivery form:	3mg and 6mg tablets
Brand owner:	Somaxon
Annual US brand sales:	Launched September 2010
First paragraph IV filing accepted by FDA:	16 September 2010
Known paragraph IV filers:	Actavis, Mylan, Par
Patents at issue – expiry dates:	6,211,229 – 17 February 2020
District court location:	New Jersey
Litigation references:	Somaxon vs Actavis *et al* 1:10-cv-01100
Other FDA Orange Book patents with expiry dates:	5,502,047 – 26 March 2013 Six other patents – 9 January 2015

Figure 1: Key details of paragraph IV challenges to Somaxon's Silenor (doxepin) insomnia remedy in the US (Source – Thomson Reuters)

FORTHCOMING NCE EXPIRIES

Brand	Active ingredient	NCE expiry date
Vyvanse	lisdexamfetamine	23 February 2012
Amturnide	aliskiren/amlodipine/HCTZ	5 March 2012
Tekamlo	aliskiren/amlodipine	5 March 2012
Tekturna	aliskiren	5 March 2012
Tekturna HCT	aliskiren/HCTZ	5 March 2012
Valturna	aliskiren/valsartan	5 March 2012
Tykerb	lapatinib	13 March 2012
Altabax	retapamulin	12 April 2012
Neupro (discont.)	rotigotine	9 May 2012
Torisel	temsirolimus	30 May 2012
Letairis	ambrisentan	15 June 2012

Figure 2: Brands listed in the US Food and Drug Administration's Orange Book with new chemical entity (NCE) exclusivities that are scheduled to expire in the first half of 2012 (Source – Thomson Reuters)