

Losartan: a modern parable of pharma patent lifecycle management

Patents and lifecycle management strategies for drug products have been under the spotlight in Europe recently. **Dr Duncan Curley** and **Dr Amanda Easey** of Innovate Legal tell the losartan story, highlighting some of the issues involved.

The controversial sector inquiry carried out by the European Commission during 2008-2009 and the decision in the AstraZeneca case recently issued by the General Court (European Union) have caused both the research-based and the generic pharmaceutical companies to reflect on their strategies for the lifecycle management of drug products. It is therefore instructive to examine some of the issues that arose when the main compound patent of a blockbuster anti-hypertensive drug – Merck's product Cozaar® (losartan) – expired in a number of major EU markets during 2010.

Anti-hypertensives – a historical perspective

By the mid-1980s, it was well established that individuals with persistent abnormally raised blood pressure, known as hypertension, are at increased risk of developing strokes, heart attacks and other cardiovascular disease. The main physiological mechanisms controlling blood pressure were also well understood. In addition to a variety of well established antihypertensive agents such as the diuretic hydrochlorothiazide ('HCTZ'), a number of new therapies became available to physicians. In particular, drugs acting on the renin-angiotensin aldosterone system, which regulates blood pressure and fluid balance, were developed as anti-hypertensives.

The renin-angiotensin hormonal cascade is initiated by the production of the enzyme renin by the kidneys. Renin acts on the protein angiotensinogen to produce the inactive protein angiotensin-I. Angiotensin-I is then converted by angiotensin-converting enzyme ('ACE') to angiotensin-II. Angiotensin-II activates angiotensin-II receptors causing blood vessels to constrict this potent vasoconstrictive action, in combination with other hormonal effects influencing fluid balance, leading to an elevation in blood pressure. Compounds which inhibit the action of ACE (and therefore the production of angiotensin-II), such as

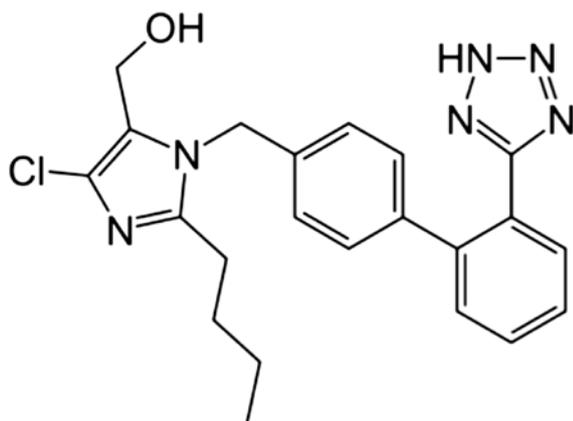
captopril and enalapril, may be used successfully as antihypertensives but a significant proportion (reportedly about 40%) of patients are non-responsive to treatment with these agents. In addition, treatment with ACE inhibitors may cause a persistent dry cough which many patients are unable to tolerate. This side effect is understood to occur as a result of the inhibition of other enzymes by the drug.

The first angiotensin-II receptor antagonist, which blocks the actions of angiotensin-II at the receptor level rather than inhibiting its production, was reported during the early 1970s. Unfortunately, this peptide compound (saralasin) was found to be ineffective when administered orally and this, in combination with the expensive production costs for peptide compounds, meant that it was not suitable for clinical development. The Japanese drug company Takeda made the discovery in 1979 that certain non-peptide, imidazole-5-acetic acid derivatives were low in toxicity and weakly suppressed the vasoconstrictive and other blood-pressure elevating actions of angiotensin-II. They showed good activity in rats, making them potentially useful as antihypertensive agents in other mammals. In the early 1980s, some patent applications of Takeda which covered this work were published¹. Then, the 'cat was out of the bag' and other pharmaceutical companies began to examine analogues of similar derivatives as potential anti-hypertensive agents.

The development of losartan by Du Pont and the collaboration with Merck

Du Pont, then a chemicals company with a relatively small business in pharmaceuticals, was the first company to modify the Takeda compounds by attaching a tetrazole functional group. Certain members of this class were found to inhibit the action of angiotensin-II at its receptors on target cells, effectively preventing the increase in blood pressure produced by the hormone/receptor interaction, including losartan.

Chemical structure of losartan



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At first, it was thought internally at Du Pont that losartan was merely a “modified” ACE inhibitor, that was unlikely to take sales from successful drugs like captopril and enalapril. Its development did not receive priority and eventually Du Pont contacted Merck to discuss the possibility of co-development². The scientists at Merck saw the potential of losartan and with their much bigger marketing muscle, they were more confident than Du Pont about launching a new, ‘first in class’ drug. Du Pont and Merck signed an agreement in 1990 to collaborate on the development of losartan. It was subsequently marketed by Merck as Cozaar. It was found that treatment with angiotensin-II receptor antagonists was not associated with the persistent dry cough which can complicate ACE inhibitor therapy. This makes them a useful alternative for patients who have to discontinue ACE inhibitor therapy as a result of this side effect. Cozaar proved to be hugely successful. Other members of this class of drug have also encountered enormous commercial success and include valsartan, irbesartan and candesartan.

The European patent³ protecting the class of compounds of which losartan was a member was due to expire on 9 July 2007, but this patent was extended in various countries by virtue of the supplementary protection scheme now set out in Regulation (EC) No. 469/2009. The expiry dates of the SPCs granted for losartan in European countries were on or around 1 September 2009.

New indications, new patents

It was soon appreciated by Merck that these compounds might have beneficial effects in the treatment of other diseases associated with hypertension. Losartan was eventually indicated for (inter alia) hypertension, the treatment of chronic heart failure, diabetic nephropathy in patients with type 2 diabetes and for reducing the risk of stroke in patients with hypertension. During the early 1990s, many of these uses of losartan for the treatment of these additional medical conditions were patented⁴, with twenty year terms lasting well beyond the expiry date of the losartan SPCs. Furthermore, combinations of losartan with diuretics were also patented and subsequently authorised as separate drug products, including Cozaar comp (or in some countries Cozaar plus), a combination of losartan and HCTZ⁵. In the UK and other European countries, separate SPCs were obtained for the combination of losartan and HCTZ, expiring on or around 14 February 2010.

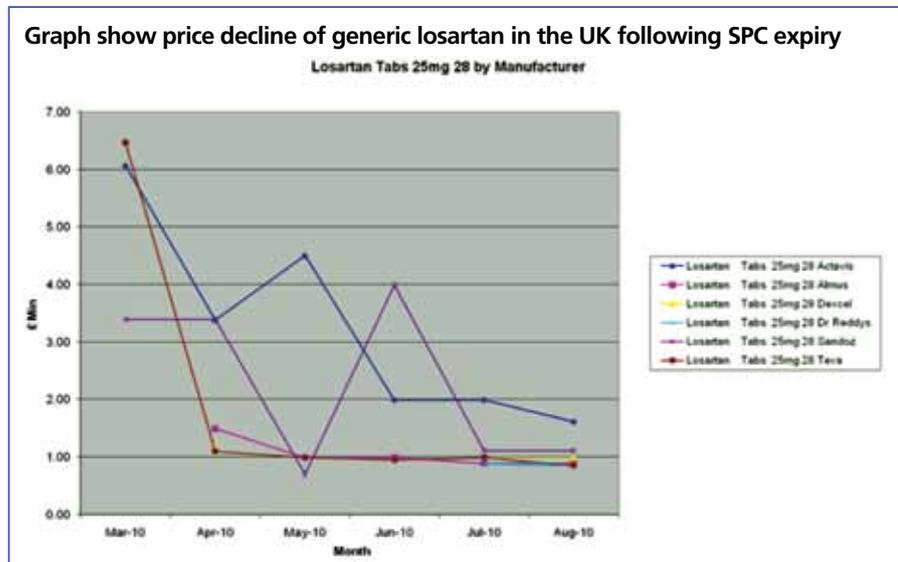
Paediatric extension

Approximately six months before the expiry of the patent on which the losartan SPC was based, in January 2007, Regulation (EC) No. 1901/2006 on medicinal products for paediatric use (“the Paediatric Regulation”) came into force. This offered the possibility of a ‘carrot’ of a further six months of exclusivity for patentees, by way of an extension to a SPC, provided that clinical trials approved by the European Medicines Agency (the EMEA) in accordance with a Paediatric Investigation Plan were carried out in children in good time before the expiry of the SPC.

By the time of the deadline for filing their application to extend the SPC (which in the UK and a number of other countries was on or around 1 March 2009), Merck had completed the trials to the satisfaction of the EMEA’s Paediatric Committee, but they had not completed certain other formalities that were prescribed in the Paediatric Regulation, which were (apparently) a precondition to the grant of the extension. This state of affairs gave rise to a refusal by the UK Intellectual Property Office to approve Merck’s paediatric SPC extension application, which was appealed first to the Patents Court and then to the Court of Appeal. At a hearing which took place on 19 August 2009 – in a courtroom packed with interested parties, including many of the generic firms for whom clarity on the SPC expiry date was clearly important – the Court of Appeal agreed to allow the six month extension for the SPC⁶.

Generic launch

All of the generic firms duly stayed off the market in the UK until the expiry of the SPC for losartan on 1 March 2010, although following expiry, a number of companies launched which resulted in a significant and immediate decline in the price of the generic product in the UK, as shown in the graph⁷ below.



It is also interesting to note that the generic competitors that launched in the UK at the beginning of March all did so with slightly different indications on the label. Some adopted a "skinny label" (with all of the patented indications removed) whereas others did not. It is not known whether Merck chose to assert contributory infringement against any of the companies who did not adopt a "skinny label" approach, but from the public record at least, it would seem not, perhaps suggesting that the patentee had recognised that the second and further medical use patents relating to losartan only had a limited value as a deterrent against the generic competition.

Patented indications aside, using the official figures for the cost of losartan to the UK NHS in the year 2009, we can estimate the value of the six month paediatric extension to Merck (in the UK alone) to be approximately £34 million (\$52 million), which gives an indication of the enormous value of the extension to the research-based companies in relation to 'blockbuster' products such as Cozaar.

An unresolved legal question – the scope of protection of a SPC

However, the story does not end there. Because of the six month paediatric extension, in a number of European countries, SPCs on the combination product (losartan and HCTZ) expired approximately two weeks before the SPC on losartan (simpliciter). While this was not an issue in the UK (because all of the generic firms stayed off the market until 1 March 2010), it raised an interesting legal question: can a SPC to losartan (alone) be used to protect against the launch of generic forms of the combination product (losartan combined with HCTZ)? There are two conflicting views. On the one hand, since a SPC is in the nature of a patent extension, any extension of the relevant patent claims to losartan would catch a combination product containing losartan and another active ingredient. The contrary argument is that a SPC is granted for a specific, identified medicinal product and the exclusion zone thus granted is restricted to generic forms of that product and not any other medicinal product.

These contrasting views were tested in Belgium and France, where, before the relevant SPC expiry dates, the multinational generic company

Mylan informed Merck that it intended to launch a product containing losartan and HCTZ after expiry of the losartan/HCTZ "combination" SPC (on or around 15 February 2010) but before the expiry of the losartan (simpliciter) SPC (on or around 2 March 2010). In France, the court adopted the former, "infringement"-type test and granted an injunction against Mylan, prohibiting the sale of the combination product in France until 2 March 2010⁸. In Belgium, the court considered that the scope of the losartan (simpliciter) SPC did not extend to Mylan's combination product⁹. It should be noted that both courts initially determined the matter on a preliminary basis, rather than at a full trial "on the merits". Nevertheless, the question of which test is correct is a vitally important one, both for the research-based and the generic pharmaceutical industries, because a number of important "combination" products are approaching their patent expiry dates in the coming years. It seems inevitable that clarification will need to be sought from the Court of Justice, at some stage.

In conclusion, the losartan story illustrates a number of hot topics that are often encountered at the end of the patent lifecycle of medicinal products in Europe, including the patenting of second and further medical indications, the scope of supplementary protection certificates (SPCs) and the six month paediatric extension that is now available.

Footnotes

1. See for example US patent 4340598, taking priority from JP applications 54-146728 and 54-146729.
2. How the antihypertensive losartan was discovered, G.Bhardwaj, Expert Opinion on Drug Discovery, 1(6), 609-618 (2006).
3. European patent no. 0,253, 310 B1.
4. See for example European patent nos. 0,533,840 B1, 0,966,282 B1 and 0,636,027 B1.
5. European patent no. 0,733,366 B1.
6. The case was reported as *E I du Pont Nemours & Co. v UK Intellectual Property Office* [2009] EWCA Civ 966.
7. Courtesy of Wavedata Ltd: www.wavedata.co.uk.
8. Tribunal de Grande Instance de Paris; decision of 12 February 2010.
9. Judgment of the Court of Appeal of Brussels (8th Chamber) of 23 February 2010.

Authors



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