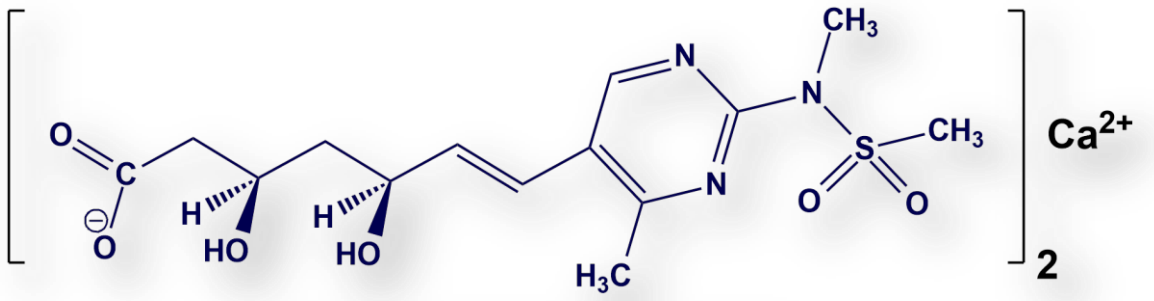
Strategies to circumvent the expiry of a patent

The pharmaceutical company AstraZeneca, manufacturer and marketer of the drug Crestor® (Rosuvastatin calcium), which diminishes cholesterol in blood plasma, is trying to prolong the patent protection of this drug a further seven years via a strategy designed to achieve "use approval" in a "rare disease" known as homozygous familial hypercholesterolemia . AstraZeneca back up their request with the Orphan Drug Act, a law drafted and adopted more than three decades ago to encourage the development of treatments for diseases with a low prevalence. This stratagem could increase the laboratory's income by several billion dollars.

Rosuvastatin calcium (Crestor®) is a cholesterol-lowering statin which technically belongs to the so-called "hidroximetilglutaril-Coenzyme-A reductase enzyme inhibitors." It is one of the most frequently prescribed drugs in its group (statins). According to IMS Health, it is the second most prescribed drug in the United States atfer levothyroxine sodium, an elective treatment for hypothyroidism.

Crestor® lost its patent protection on 8 July, 2016, opening the doors to the emergence of generic versions of the drug.



CALCIUM ROSUVASTATIN

Calcium (3*R*,5*S*,*E*)-3,5-dihydroxy-7-(4-methyl-2-(*N*-methylmethylsulfonamido)pyrimidin-5-yl)hept-6-enoate

Crestor® has been a real blockbuster for AstraZeneca. Of the 23.6 billion-dollar profit of this British multi-national in 2013, 5 billion came from the sales of Crestor®. The

importance of the US pharmaceutical market is evident when you consider that 2.8 billion of these sales corresponded to the United States alone, where the monthly cost of treatment with this statin is $260 (information GoodRx.com).

This application for a prolongation of the drug's patent protection caused controversy which began in May, 2016 when AstraZeneca gained approval for the treatment of patients with homozygous familial hypercholesterolemia. The Food and Drug Administration approved an extension of the patent for seven more years, exclusively for this use.

We should bear in mind that the information about this use of Rosuvastatin calcium in homozygous familial hypercholesterolemia may not appear on the prospectus of generic versions for at least the next seven years. Generic Rosuvastatin calcium may include all other uses of Crestor®.

The dose required for the treatment of homozygous familial hypercholesterolemia is different from that required for the rest of the approved indications.

AstraZeneca has argued that if generic versions of Rosuvastatin calcium are authorized, prescription errors seriously affecting the safety of the drug may occur.

Michele Meixell, an AstraZeneca spokeswoman, said the drug company pursued this new use of Crestor®as "part of our standard practice to address unmet needs".

Spectrum Pharmaceuticals lost a lawsuit in May 2016 when they tried to prevent the marketing of generic versions of the drug Fusilev® (calcium Levofolinate).

Otsuka Pharmaceutical recently tried to protect their antipsychotic drug Aripiprazole (Abilify®) in the same way against the marketing of generic versions. The FDA approved generic versions of Aripiprazole in April, 2016, although Otsuka Pharmaceutical appealed against the decision.

Perhaps the most famous case of these attempts to prolong patent protection was when Bristol Myers Squibb tried for three years to extend the patent for Glucophage (Metformin), the most frequently prescribed drug as a first-line treatment of type 2 diabetes (adult onset diabetes). Regarding the Orphan Drug Act, in the court order it was established that "[the] extension of exclusivity via loopholes in the law should never be allowed to harm those who consume pharmaceutical products".

AstraZeneca has been studying the use of Crestor® in the paediatric population for some years. However, in 2014, they initiated a clinical trial on children aged between 6 and 17 who had been diagnosed with homozygous familial hypercholesterolemia.

In the United States the number of children affected by this condition ranges from 300 to 1,000. The disease occurs when a child inherits two mutated alleles, one from the father and one from the mother. One result is very high plasma cholesterol concentrations with its associated risks, including heart attacks, even during childhood. Many children with this condition have to undergo a process similar to dialysis several times a week to clear their arteries of excess cholesterol.

A clinical trial being conducted by AstraZeneca involves only 14 children who receive a daily dose of Rosuvastatin calcium. After 6 weeks, the group of children taking this drug (the study group) showed a reduction in LDL-cholesterol levels significantly greater than the placebo group. The result of the study was predictable, since statins are a cornerstone of the treatment of homozygous familial hypercholesterolemia.

Many contend that AstraZeneca has delayed carrying out a study on this "rare disease" until now, when they could have acted earlier. The laboratory has shown an unusual interest in carrying out this clinical trial only when the patent was about to expire. Besides, the drug continues to be fully effective as a first-line of treatment.

A generic version of Crestor®, sold by Allergan, an American company which moved its headquarters to Dublin, Ireland, last May (2016), was marketed amid a dispute with AstraZeneca. However, prices of Rosuvastatin calcium will only decrease significantly when a sufficient number of generic versions appear on the market.

The extension of patent protection in order to temporarily prevent competition from generic versions was debated in the US Congress. Last year (2015), the 21st Century Cures Act was passed in order to give an extra six months of protection against competition from generic versions of those drugs that had been approved specifically for the treatment of 'rare diseases'.

Max G. Bronstein, director of EveryLife for Rare Diseases Foundation, has supported the extension of the terms of patent protection; an indirect way of stimulating the development of new drugs for rare diseases because, by doing this, the profits of

pharmaceutical companies increase. However, this procedure will further increase the pharmaceutical bill, compromising the viability of private and public health systems. Let us not forget that treatment of hypercholesterolemia will almost certainly experience a great leap forward with the emergence of a new pharmacological group: the "PCSK9 enzyme inhibitors." The first two are Arilocumab and Evolocumab.

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