

*newsletter***Drug product withdrawal****Vioxx**

On 30 September 2004, the manufacturer of the drug Vioxx® (active ingredient: Rofecoxib) voluntarily withdrew the product from the market. In 2003 alone, the revenue generated by this pain-relief medication amounted to around US\$ 2.55 bn.

Introduction

Many millions of people around the world rely on "non-steroidal anti-inflammatory drugs" (NSAIDs) for the control of pain and inflammatory illness. The world market volume of prescription NSAIDs is put at around US\$ 12 billion. What are known as selective COX-2 inhibitors (coxibs) are a relatively new class of substance within the NSAID therapeutic group, with annual sales in 2003 in the order of US\$ 6 billion.

COX-2 inhibitors currently on the market ¹

Active ingredient	Brand name [®]	Approval in Germany	COX 2 selectivity ²
Rofecoxib	Vioxx, Vioxx Dolor, Ceox	1999 (global recall, Oct. 2004)	35
Celecoxib	Celebrex, Celebra, Onsenal	2000	6.6-7.5
Valdecoxib	Bextra, Valdyn	2003	30
Parecoxib ³	Dynastat, Rayzon	2002	30
Etoricoxib	Arcoxia	2004	106

¹ Lumiracoxib (Prexige®) has been on the market in eg the UK since 2004; approval in Germany planned for 2005

² (COX-1:COX-2 IC₅₀), the higher the number, the higher the COX-2 selectivity

³ Parecoxib is metabolised quickly in the liver to form Valdecoxib

Pain relievers (NSAIDs), Cyclooxygenase enzymes, Effect

The messenger function performed by prostaglandins is important in the development of pain and the inflammatory process. Prostaglandins are synthesised from arachidonic acid with the help of, among other things, the cyclooxygenase enzyme (COX). COX has been discovered to have two isoforms, COX-1 and COX-2. Apart from their role in pain development, both forms perform other specific duties in the human body. In particular, COX-2 enzymes are responsible for increasing the production of prostaglandins in response to inflammation and pain, the stimulus being transmitted to the central nervous system via peripheral nerves.

For the most part, NSAIDs work by inhibiting the formation of cyclooxygenase enzymes (COX-1 and COX-2 enzymes) and, thus, by blocking the transmission of the pain stimulus by the prostaglandins. Tried and tested drugs include Ibuprofen, Diclofenac, Meloxicam and the active ingredient of Aspirin (ASA). These inhibit, in the main, COX-1 enzymes. However, these medications are known to cause adverse side-effects in the stomach and the gastrointestinal tract (dyspepsia, heartburn, stomach ulcers, bleeding).

**Selective
COX-2 inhibitors,
Cardio-vascular
events**

Drugs which selectively inhibit COX-2 enzymes (COX-2 inhibitors) were developed in the hope of reducing the frequency and severity of known adverse gastrointestinal side-effects produced by conventional NSAIDs, above all during the treatment of chronic rheumatic disease. Positive effects were indicated in studies involving two coxibs (VIGOR: Rofecoxib versus Naproxen, CLASS: Celecoxib versus Diclofenac or Ibuprofen). The results of these studies led the authorities to declare that the benefits of such drugs outweighed the risks.

With regard to adverse side-effects, particular attention was paid to cardiovascular events including heart attacks and strokes. Since their approval, COX-2 inhibitors – and above all Vioxx® (Rofecoxib) – have been suspected of displaying a potential cardiovascular risk greater than that found in conventional NSAIDs. Although patients' attention was drawn to the risk via the information leaflet, comparative data captured in long-term, placebo-controlled studies was not available at this time.

Then, in APPROVe - a randomised, placebo-controlled, double-blind study - the effect of 3 years of treatment with Rofecoxib on the recurrence of polyps of the large bowel in patients with a history of colorectal adenomas was analysed. In the APPROVe study, there was an increased - albeit relatively low - incidence (0.75 events/100 patient years for placebo, 1.48 events/100 patient years for Rofecoxib) for confirmed cardiovascular events, such as heart attacks and stroke, beginning after 18 months of treatment. For this reason, the trial was aborted eight weeks before it was due to close. Then, in October 2004, the manufacturer voluntarily withdrew all drugs containing Rofecoxib (Vioxx®) from the market. According to the manufacturer's own data, the drug had been prescribed to more than 90 million patients since first being marketed, with annual sales amounting to some US\$ 2.55 billion.

Whether there is a class effect here, ie all the drugs belonging to the group of COX-2 inhibitors carrying the same risk as Vioxx, has yet to be determined.

**Approval of
drugs,
Clinical trials**

New drugs are obliged to undergo a much more elaborate and indeed costlier process of approval prior to licensing than other products. The official process draws on the results of studies to document the quality, efficacy, toxicology and safety of the new product. Using test persons and patients, the studies aim to ascertain the safety and compatibility of a drug, its efficacy and side-effects, and how the active ingredient in question metabolises in the human body. As a rule, the efficacy of each indication stated in the application compared with placebo and/or effective standard therapy must be established. The time from the discovery of an active ingredient to market maturity is typically 10 - 15 years. Medical products are tested in trials that can involve as many as 15,000 patients. The costs can be as high as US\$ 800 million.

**Drug safety,
Adverse side-
effects**

On the basis of the clinical trials, the relevant authorities (in Germany, the BfArM; in the USA, the FDA) decide whether or not to approve a product. Generally it can be said that new products have an excellent standard of safety today. Yet despite the stringent criteria, adverse and, in some cases, serious side-effects often manifest themselves only after the product has entered the market. Such effects become especially conspicuous when a new drug is prescribed to millions of patients within a short space of time or - in the case of a chronic illness - over many years. Especially with the latter case, long-term clinical experience is often not available.

Examples of withdrawals and/or bans affecting blockbuster drugs

Below is a list of so-called blockbuster drugs that have been either banned or voluntarily withdrawn by the manufacturer due to adverse side-effects. Blockbuster drugs are those which have recorded very high sales figures (eg US\$ 500 million) and been prescribed to several millions of people.

Active ingredient	Brand name ®	Use	with-drawn	Reason
Thalidomide ¹	Thalidomid	Sedative/morning sickness	1961	Birth defects
Cisapride	Propulsid	Unspec. gastro-intestinal problems	2000	Irregular heart rhythm (fatal)
Troglitazone	Rezulin	Diabetes mellitus	2000	Liver toxicity
Cerivastatin	Baycol, Lipobay	Anti-cholesterol	2001	Rhabdomyolysis
Rofecoxib	Vioxx	Pain relief	2004	Stroke, heart attack

¹Since the recall of the drug Thalidomid, pharmaceutical manufacturers in Europe have had to provide the relevant authorities with evidence from clinical trials that their products are safe

Relevance for underwriters

When a medical product is withdrawn or banned, the product liability insurer may be faced with serious financial losses. Due to the many new fields of application and new medical findings, even a largely positive risk/benefit appraisal after highly stringent approval criteria is no guarantee that a drug will not be recalled from the market. This aspect should always be considered when assessing the risk inherent in newly licensed pharmaceutical products. An analysis of past recalls involving pharmaceutical products highlights the specific, risk-aggravating factors listed below. These can be used also as a basis for evaluating a particular risk:

- the drug is new on the market,
- the drug is being used to combat a chronic, widespread disease for which manifold tried-and-tested alternatives already exist,
- the drug has been prescribed to many patients within a very short space of time,
- the drug represents an entirely new medical approach,
- the product can be regarded as a "pseudo innovation",
- the manufacturer is one of the giants in the sector,
- the drug is a "lifestyle drug",
- the drug has been sold many times in the USA.

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