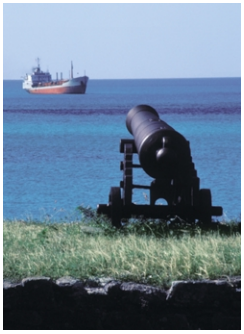
COXIBs on TARGET?

Sue Lyon, Science writer



Industry watchers intrigued by the absence of Merck Sharp & Dohme (MSD) from the 12th United European Gastroenterology Week (UEGW), which ended in Prague on 29 September, had their curiosity satisfied the next day when the company announced the global withdrawal of its COX-2 selective inhibitor ('coxib') rofecoxib. This event has cast doubts on the class as a whole, and could have important general implications for drug development.

APPROVe

MSD's decision was triggered by results of the APPROVe study. In this placebo-controlled trial, designed to investigate the drug's effect on benign sporadic adenomas, patients taking rofecoxib were at double the risk of serious thromboembolic events including myocardial infarction (MI) – a risk that became apparent only after 18 months' treatment.

Pfizer, which had a strong presence at UEGW, has rejected suggestions of a class effect and has robustly defended the cardiovascular safety of its coxibs, celecoxib, parecoxib and valdecoxib. Novartis has been similarly positive about lumiracoxib, which is yet to be launched but has been approved by the UK acting as reference member state under the European mutual recognition procedure.

The viability of a class

According to a Novartis spokesman: 'A number of drugs have been pulled from the market in the past, raising questions after the viability of a class. This includes the NSAIDs back in the 1980s, type-2 diabetes drugs when troglitazone was withdrawn, the statins with cerivastatin, and also terfenadine for the antihistamine class. We have proven with the TARGET study that lumiracoxib – even at two or four times the recommended daily dose – offered significant gastrointestinal benefits without increased cardiovascular risk.'

TARGET compared lumiracoxib with ibuprofen and naproxen, and was specifically designed to investigate the gastrointestinal, cardiovascular, renal and hepatic safety of lumiracoxib. Presenting TARGET results [1] at UEGW, Professor Chris Hawkey, University of Nottingham, UK (http://www.nottingham.ac.uk) reported: 'In the overall population there was no difference in the cumulative Anti-Platelet Trialists Collaborative (APTC) endpoint, and when we looked at individual APTC endpoints there was no significant difference in the results.'

The EMEA follows suit

Hawkey speculated that lumiracoxib might have advantages over other coxibs because of its unique molecular structure, preferential distribution to inflamed synovial tissue and short plasma half-life. However, critics have continued to question the drug's cardiovascular safety; even TARGET, with over 18,000 patients, was not powered to detect a statistically significant difference in rates of MI between the study arms.

As a precautionary measure, the European Medicines Agency (EMEA) is to examine all aspects of the cardiovascular safety of the coxibs, including thrombotic (MI and stroke) and cardiorenal events (hypertension, oedema and cardiac failure). The objective is to assess whether changes are required to marketing authorizations and additional studies are needed. This announcement follows the FDA decision to review the cardiovascular safety profile of the coxibs, and this will also include consideration of suitable forms of pre- and post-marketing evaluation.

Pharmacovigilence

Until the regulatory agencies report, clinicians might in the short term prefer to return to the devils they know by coprescribing a traditional NSAID with a gastroprotective agent, and the advantages of this strategy were confirmed at UEGW [2]. In the longer term, prescribers might have alternatives in developmental drugs such licofelone, a dual inhibitor of 5-LOX/COX, and COX-inhibiting nitric oxide donors (CINOD) such as AZD3582, which was associated with significantly less gastrointestinal toxicity than naproxen in a healthy volunteer study reported in Prague [3]. However, as the withdrawal of rofecoxib has also inspired calls for general measures to improve pharmacovigilance [4,5], treatments for arthritis and other non-life-threatening disorders could in future face more demanding scrutiny throughout their development.

References

1 Schnitzer, T.J. *et al.* (2004) Therapeutic Lumiracoxib Arthritis Research and Gastrointestinal Event Trial (TARGET) – reduction in ulcer complications with lumiracoxib compared with naproxen and ibuprofen. *Gut* 53 (Suppl VI), A36

2 Jones, R. *et al.* (2004) Esomeprazole reduces gastric and duodenal ulcer incidence in at-risk patients taking continuous NSAID therapy. *Gut* 53 (Suppl VI), A36

3 Wilder-Smith, C.H. *et al.* (2004) Upper gastrointestinal tract muscosal injury by AZD3582, a COX-inhibiting nitric oxide donor (CINOD), a randomised, double-blind, cross-over study in healthy subjects. *Gut* 53 (Suppl VI), A36

4 Dieppe, P.A. *et al.* (2004) Lessons from the withdrawal of rofecoxib. *Br. Med. J.* 329, 867–868

5 Anon. (2004) Vioxx: an unequal partnership between safety and efficacy. *Lancet* 364, 287–288

1359-6446/04/$ – see front matter PII: S1359-6446(04)03290-8