

Theme Issue Article

Selective COX-2 inhibitors and risk of thromboembolic events – regulatory aspects

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Summary

In the 1990s, the pharmaceutical industry developed selective COX-2 inhibitors (coxibs) as alternatives to conventional non-steroidal anti-inflammatory drugs (NSAIDs), with the expectation of similar analgetic and anti-inflammatory efficacy but a reduced risk of adverse gastrointestinal (GI) effects. Marketing authorisation (MA) was granted for rofecoxib and celecoxib as first representatives of this new pharmacological class at the end of the 1990s in the EU. In the following years MAs were granted for the 'second generation' coxibs etoricoxib, parecoxib/valdecoxib and lumiracoxib. However, data from large clinical 'outcome studies' as well as epidemiological data raised concerns

about the cardiovascular (CV) safety of the coxibs. In consequence, two comprehensive review processes (referrals) were initiated by the European Medicines Agency (EMA). As a result, in the EU the use of coxibs has been contraindicated in patients with established coronary heart disease, cerebrovascular disease and peripheral arterial disease and a number of warning statements concerning CV, GI and skin toxicity have been introduced in the coxib product informations. This article provides a description of the regulatory actions taken and discusses some specific aspects of the past and future regulatory assessment of coxibs.

Keywords

Cyclooxygenase 2 inhibitors, anti-inflammatory agents, non-steroidal, cardiovascular diseases, gastrointestinal diseases, legislation, drug

Thromb Haemost 2006; 96: 423–32

Scientific rationale for development of selective COX-2 inhibitors by the pharmaceutical industry

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in medical practice for the symptomatic treatment of acute pain and chronic inflammatory and degenerative joint diseases such as rheumatoid arthritis (RA) and osteoarthritis (OA). However, their use has been restricted by the occurrence of gastrointestinal (GI) adverse events, including gastric and duodenal ulcers, sometimes associated with serious complications such as perforations, obstructions and bleedings, which may result in fatal consequences in some cases.

The analgetic, antipyretic and anti-inflammatory effects as well as the serious adverse GI effects of NSAIDs are believed to be mainly related to an inhibition of prostaglandin synthesis via inhibition of the enzyme cyclooxygenase (COX).

In the early 1990s it was recognized that at least two COX isoenzymes, COX-1 and COX-2, exist. As the knowledge about

the physiological and pathophysiological properties of these COX isoenzymes increased, the hypothesis was put forward that selective COX-2 inhibitors would have analgetic and anti-inflammatory properties, however, be devoid of (or have a much lower risk for) adverse GI effects. This hypothesis was based on the assumption that COX-2 is mainly induced by pro-inflammatory stimuli and primarily responsible for the synthesis of prostanoïd mediators of pain, inflammation and fever, whereas COX-1 appeared to be a mainly constitutive enzyme and responsible e.g. for synthesis of GI prostanoids involved in protection of the GI mucosa against harmful stimuli.

'Regulatory history' of selective COX-2 inhibitors in the EU

This hypothesis led to the development of a number of selective COX-2 inhibitors by the pharmaceutical industry, which finally resulted in the application for marketing authorisation (MA) for

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Received August 24, 2006
Accepted after revision September 6, 2006

Prepublished online September 13, 2006 doi:10.1160/TH06-08-0462

Table 1: 'Regulatory history' of the coxibs in the EU. Date of first marketing authorisation resp. redrawing/suspension of coxibs in the EU, of EMEA coxib referrals, of related EMEA press releases* and of publication of coxib outcome studies. For details of EMEA press releases see Appendix.

Year	First marketing authorisation in the EU	Marketing redrawl/suspension	Coxib outcome studies	EMEA coxib referrals	EMEA press releases*	
1999	10/1999 Rofecoxib MRP MA Ind: OA and RA					
	12/1999 Celecoxib National MA: Sweden Ind: OA and RA					
2000			CLASS (C v D/I) VIGOR (R v N)			
2001	10/2001 Etoricoxib National MA UK Ind: OA, RA and pain in acute gouty arthritis		ADVANTAGE (R v N) SUCCESS (C v D/N)			
	12/2001 Rofecoxib MRP MA Ind: Acute pain, pain in primary dysmenorrhea					
2002	03/2002 Parecoxib Central EU MA Ind: Acute pain		CABG-I (P/V v Pla)	07/2002 First Coxib Referral	22.10.2002 Parecoxib: hypersensitivity and skin reactions ¹	
2003	03/2003 Valdecoxib Central EU MA Ind: OA, RA, acute pain in dental surgery and primary dysmenorrhea					
	09/2003 Lumiracoxib National MA: UK. Ind: OA, acute pain in dental and orthopaedic surgery and primary dysmenorrhea					
	10/2003 Celecoxib Central EU MA Ind: FAP					
2004		30/09/2004 Rofecoxib Voluntary worldwide withdrawal	EDGE (E v D) TARGET (L v D/N) APPROVe (R v Pla) CABG-II (P/V v Pla) APC (C v Pla) PreSAP (C v Pla) ADAPT (C/N Pla)	04/2004 Referral finalisation by European Commission	30/04/2004 CPMP Opinion on coxibs ² 06/10/2004 Statement following withdrawal of rofecoxib ³ 22/10/2004 EMEA to review coxibs ⁴ 15/12/2004 Public statement on parecoxib and valdecoxib ⁵ 17+22/12/2004 Statements on celecoxib ^{6,7}	
				22/10/2004 Second Coxib Referral		

Table 1: Continued

Year	First marketing authorisation in the EU	Marketing redrawing/suspension	Coxib outcome studies	EMEA coxib referrals	EMEA press releases
2005	10/1999 Rofecoxib MRP MA Ind: OA and RA 12/1999 Celecoxib National MA: Sweden Ind: OA and RA	01/2005 Onsenal (Celecoxib) voluntary withhold of marketing 04/2005 Bextra (Valdecoxib) Temporary suspension of MA 08/2005 Withdrawal of the MA of Valdyn (Valdecoxib)	ADAPT (C/N v Pla)	10/2005 Referral finalisation by European Commission	20/01/2005 Update on coxibs ⁸ 17/02/2005 Statement on coxibs ⁹ 07/04/2005 Suspension of use of Bextra ¹⁰ 27/06/2005 Conclusion of action on coxibs ^{11, 12} 02/08/2005 Review of safety of non-selective NSAIDs ^{13, 14} 11/08/2005 Withdrawal of the MA of Val-dyne ¹⁵ 17/10/2005 Update on non-selective NSAIDs (key elements) ¹⁶⁻¹⁸
				27/10/2005 Suspension of MA of Bextra ¹⁹ 09/11/2005 COX-2 inhibitors in veterinary medicine ²⁰ 28/11/2005 CHMP opinion on coxibs following a referral ²¹	

Abbreviations used:

Drug names: C = celecoxib, D = diclofenac, E = etoricoxib, I = ibuprofen, L = lumiracoxib, N = naproxen, P = parecoxib, R = rofecoxib, V = valdecoxib, Pla = placebo; **Outcome studies:** ADAPT: Alzheimer's Disease Anti-Inflammatory Prevention Trial (17), ADVANTAGE: Assessment of Difference between Vioxx and Naproxen to Ascertain Gastrointestinal Tolerability and Effectiveness (52), APC: Adenoma Prevention with Celecoxib (8), APPROVe: Adenomatous Polyp Prevention on Vioxx (5), CABG-I+I: Coronary artery graft bypass studies (10-12), CLASS: Celecoxib Long-term Arthritis Safety Study (3), EDGE: Etoricoxib Diclofenac Gastrointestinal Investigation Study (15,16), PreSAP: Prevention of Spontaneous Adenomatous Polyps (9), SUCCESS: Successive Celecoxib Efficacy and Safety Studies (53), TARGET: Therapeutic Arthritis Research and Gastrointestinal Event Trial (13,14), VIGOR: Vioxx Gastrointestinal Outcomes Research (4); **Other abbreviations:** MA = marketing authorisation, MRP = mutual recognition procedure, CHMP = Committee for Medicinal Products for Human Use.

celecoxib and rofecoxib as first representatives of the new pharmacological class of the so-called 'coxibs' at the end of the 1990s in the USA and in the EU (see Table1).

Quite early during the drug development process of selective COX-2 inhibitors, concerns were spelled out that this pharmacological class might be intrinsically associated with an increased risk of thromboembolic events in treated patients. Several hypotheses were put forward as scientific basis of these concerns. The most prominent of these concluded that a disturbance of the endogenous prostacyclin/thromboxane balance by selective COX-2 inhibitors, which were expected to inhibit the synthesis of 'antithrombotic' prostacyclin (by endothelial cells) and to leave the COX-1-dependent synthesis of the 'prothrombotic' thromboxane (by platelets) unaffected, would result in an increased risk of thromboembolic events. However, since then, it has become increasingly clear that prostacyclin may not only op-

pose potential prothrombotic effects of thromboxane but may act as a general constraint on multiple thrombosis stimuli via different mechanisms of action (1, 2).

These concerns were intensively discussed during the MA procedure of celecoxib and rofecoxib. However, the non-clinical and clinical data submitted for MA application did not point to an increased risk of thromboembolic events in coxib-treated patients. On the other hand, celecoxib and rofecoxib proved to be effective in the claimed indications and evidence for an improved GI tolerability was for example derived from placebo- and active comparator-controlled short-term endoscopic studies. Therefore, the benefit/risk balance was considered positive and MAs for celecoxib and rofecoxib were granted in the EU for the symptomatic treatment of patients with chronic inflammatory and degenerative diseases such as RA and OA. Subsequently, rofecox-

ib received MA for treatment of acute pain and pain associated with primary dysmenorrhoea in the EU.

During the following years, a number of 'second generation' coxibs were granted MA in the EU. Etoricoxib received MA for rheumatic diseases, including gouty arthritis in some EU member states. Valdecoxib was granted MA via the EMEA central procedure for treatment of RA and OA and pain associated with primary dysmenorrhoea. Parecoxib, a prodrug of valdecoxib, was granted MA via the central EMEA procedure for short-term treatment of post-surgical pain, when used intravenously or intramuscularly. Finally, lumiracoxib received MA (currently only in the UK) for symptomatic treatment of OA and acute pain associated with dental and orthopaedic surgery and primary dysmenorrhoea. In addition, celecoxib was granted a MA for an orphan drug indication (familial adenomatous polyposis) via the EMEA central procedure (see Table 1).

Since the data submitted for MA did not provide definite proof that serious adverse GI events were indeed significantly reduced under therapy with coxibs when compared with conventional NSAIDs, the involved pharmaceutical companies initiated large post-approval studies to show the GI benefit of celecoxib (CLASS study) (3) and rofecoxib (VIGOR study) (4) in comparison with selected non-subtype specific COX inhibitors.

It were data from the VIGOR study which raised serious concerns about the cardiovascular (CV) safety of rofecoxib and of the pharmacological class of selective COX-2 inhibitors in general. Although primarily designed to show a GI benefit of rofecoxib in comparison with naproxen, the results indicated a significantly increased risk of adverse CV thromboembolic events, particularly myocardial infarction (MI), in rofecoxib-treated patients. Several hypothesis were offered to explain the outcome of the VIGOR study, including an assumed cardioprotective effect of naproxen, related to an inhibitory effect on thrombocyte aggregation, similar to the one well-known for low-dose acetylsalicylic acid (ASA).

From a regulatory point of view, the VIGOR study, together with epidemiological data, which also raised concerns about the CV safety of coxibs, constituted the starting point for a reconsideration of the benefit/risk balance of the coxibs approved at that point of time (celecoxib, etoricoxib, parecoxib, rofecoxib, valdecoxib) with respect to adverse CV and GI effects in an EU-wide EMEA referral procedure initiated in July 2002. An assessment of serious hypersensitivity reactions (e.g. anaphylaxis and angioedema) and serious adverse skin reactions (including Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme and exfoliative dermatitis) was added in October 2002, based on concerns raised by epidemiological data.

As a result of this first EU coxib-referral, the European Commission concluded in April 2004 that the benefit/risk balance of the coxibs remained favourable, however, that additional warnings should be added to the product informations concerning CV safety (mainly concerning the risk of MI), GI safety (mainly concerning the association with ASA) and observed or potential serious skin effects and hypersensitivity reactions and that the sections on undesirable effects and pharmacodynamic properties should be updated accordingly.

In September 2004, Merck, Sharp & Dohme announced the world-wide, voluntary withdrawal of rofecoxib on basis of data

from the APPROVe study (5), which had shown an increased risk of thromboembolic events, particularly MI, in patients treated for more than 18 months with rofecoxib in comparison with placebo-treated patients. [Meanwhile, a statistical re-evaluation of the APPROVe data indicates that an increase in adverse CV events is observable as early as after nine months of treatment (6)].

In consequence, a second EMEA referral was initiated in October 2004 for the coxibs still approved at that point of time in the EU (celecoxib, etoricoxib, lumiracoxib, parecoxib, valdecoxib). During this referral, data from large post-approval studies, which had meanwhile become available [CLASS (3), SUCCESS (7), ACP (8), PreSAP (9) for celecoxib, two CABG studies (10–12) for parecoxib and valdecoxib, TARGET (13, 14) for lumiracoxib, EDGE (15, 16) for etoricoxib; see Table 1] and the most recent epidemiological data were taken into account.

This referral resulted in the following regulatory recommendations, decisions and opinions:

- the pharmacological class of coxibs appears to be associated with an increased risk of CV adverse effects (including MI and stroke)
- the benefit/risk balance of valdecoxib was considered to be negative in comparison to the other assessed coxibs because of the occurrence of a higher rate of serious adverse skin reactions such as Stevens-Johnsons syndrome and toxic epidermal necrolysis, some with fatal consequences. In consequence, the MA for valdecoxib was suspended for at least one year to give the MA holder the opportunity to provide additional data
- for the other involved coxibs, the benefit/risk balance was considered to remain positive, provided that a number of contraindications and warnings were introduced in the coxib product informations to exclude, respectively restrict the use of these medicinal products by specific high-risk patient subpopulations (for details see also Table 2):
- contraindications stating that COX-2 inhibitors must not be used in patients with established ischaemic heart disease, cerebrovascular disease (stroke), and peripheral arterial disease
- reinforced warnings to healthcare professionals to exercise caution when prescribing coxibs to patients with risk factors for heart disease, such as hypertension, hyperlipidaemia (high cholesterol levels), diabetes and smoking
- given the association between CV risk and exposure to coxibs, doctors are advised to use the lowest effective dose for the shortest possible duration of treatment
- additional or strengthened warnings to healthcare professionals and patients that hypersensitivity reactions and rare, but serious and sometimes fatal skin reactions can occur with all coxibs. In the majority of cases these occur in the first month of use, and prescribers are warned that patients with a history of drug allergies may be at greater risk.

Subsequent to the assessment of coxibs, the benefit/risk balance of conventional NSAIDs was also reviewed by the EMEA, since recent clinical [ADAPT study (17)] and epidemiological data (18, 19) raised concerns about the CV safety of these medicinal products as well. No immediate regulatory actions have been

Table 2: Common wording for the product information of coxibs following the two EU coxib-referrals.

Cardiovascular safety	Section 4.2: Posology and method of administration	As the cardiovascular risks of <invented name> may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis.
	Section 4.3: Contraindication	Established ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease. Congestive heart failure (NYHA II-IV).
	Section 4.4: Special warnings and precautions	As the cardiovascular risks of <coxib> may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis. Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with <coxib> after careful consideration. COX-2 selective inhibitors are not a substitute for ASA for prophylaxis of cardiovascular thrombo-embolic diseases because of their lack of antiplatelet effects. Therefore, antiplatelet therapies should not be discontinued. As with other drugs known to inhibit prostaglandin synthesis fluid retention and oedema have been observed in patients taking <coxib>. Therefore, <coxib> should be used with caution in patients with history of cardiac failure, left ventricular dysfunction or hypertension, and in patients with preexisting oedema from any other reason, since prostaglandin inhibition may result in deterioration of renal function and fluid retention. Caution is also required in patients taking diuretic treatment or otherwise at risk of hypovolaemia.
	Section 4.5: Interactions with other drugs and other forms of interaction	<Coxib> can be used with low-dose ASA but is not a substitute for ASA for cardiovascular prophylaxis. In the submitted studies, as with other NSAIDs, an increased risk of gastrointestinal ulceration or other gastrointestinal complications compared to use of <coxib> alone was shown for concomitant administration of low-dose ASA
	Section 5.1: Pharmacodynamic properties	The difference in antiplatelet activity between some COX-1 inhibiting NSAIDs and COX-2 selective inhibitors may be of clinical significance in patients at risk of thromboembolic reactions. COX-2 selective inhibitors reduce the formation of systemic (and therefore possibly endothelial) prostacyclin without affecting platelet thromboxane.
Gastrointestinal safety	Section 4.3: Contraindication	Active peptic ulceration or gastrointestinal (GI) bleeding.
	Section 4.4: Special warnings and precautions	Upper gastrointestinal complications [perforations, ulcers or bleedings (PUBs)], some of them resulting in fatal outcome, have occurred in patients treated with <coxib>. Caution is advised with treatment of patients most at risk of developing a gastrointestinal complication with NSAIDs; the elderly, patients using any other NSAID or ASA concomitantly or patients with a prior history of gastrointestinal disease, such as ulceration and GI bleeding. There is further increase in the risk of gastrointestinal adverse effects for <coxib> (gastrointestinal ulceration or other gastrointestinal complications), when <coxib> is taken concomitantly with ASA (even at low doses). A significant difference in GI safety between selective COX- 2 inhibitors + ASA vs. NSAIDs + ASA has not been demonstrated in long-term clinical trials.
	Section 5.1: Pharmacodynamic properties	Cyclooxygenase is responsible for generation of prostaglandins. Two isoforms, COX-1 and COX-2, have been identified. COX-2 is the isoform of the enzyme that has been shown to be induced by proinflammatory stimuli and has been postulated to be primarily responsible for the synthesis of prostanoid mediators of pain, inflammation, and fever. COX-2 is also involved in ovulation, implantation and closure of the ductus arteriosus, regulation of renal function, and central nervous system functions (fever induction, pain perception and cognitive function). It may also play a role in ulcer healing. COX-2 has been identified in tissue around gastric ulcers in man but its relevance to ulcer healing has not been established.
Skin reactions	Section 4.4: Special warnings and precautions	Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of <coxib> (see 4.8). Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first month of treatment. Serious hypersensitivity reactions (anaphylaxis and angioedema) have been reported in patients receiving <coxib> (see 4.8). Patients with a history of any drug allergy may be at greater risk of serious skin reactions or hypersensitivity reactions (see 4.3). <Coxib> should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

considered necessary by the EMEA as a result of this review. However, to achieve an EU-wide harmonisation, the presence of a number of so-called 'key elements' concerning CV, GI and skin toxicity in the product informations of the conventional NSAIDs has been recommended (see Table 3).

Specific aspects of the regulatory assessment of the prothrombotic potential of coxibs

Non-clinical aspects

The coxibs have been evaluated by the 'standard package of non-clinical safety pharmacology and toxicological studies. However, while these studies have been helpful to characterize their

Table 3: 'Key elements' for the product information of non- selective NSAIDs¹.

Gastrointestinal safety	Section 4.3: Contraindication	history of GI bleeding or perforation, related to previous NSAIDs therapy active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct periods of proven ulceration or bleeding)
	Section 4.4: Special warnings and precautions	the use of <invented name> with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided. undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms elderly: the elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal. gastrointestinal bleeding, ulceration and perforation: GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events. ?the risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (See section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose ASA, or other drugs likely to increase gastrointestinal risk. patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment. Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as ASA (See section 4.5). when GI bleeding or ulceration occurs in patients receiving <Invented name>, the treatment should be withdrawn. NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated (see section 4.8).
	Section 4.5: Interactions with other drugs and other forms of interaction	corticosteroids: increased risk of gastrointestinal ulceration or bleeding (see section 4.4) Anti-coagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4). anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4).
	Section 4.8: Undesirable effects	gastrointestinal: the most commonly observed adverse events are GI in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following administration. Less frequently, gastritis has been observed.
Cardiovascular safety	Section 4.3: Contraindication	severe heart failure
	Section 4.4: Special warnings and precautions	caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with NSAID therapy.
	Section 4.8: Undesirable effects	oedema, hypertension and cardiac failure have been reported in association with NSAID treatment.
Skin reactions	Section 4.4: Special warnings and precautions	serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. <Invented name> should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.
	Section 4.8: Undesirable effects	bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis (very rare).

¹: as adopted by the CHMP in October 2005 (EMA/CHMP/343456/2005).

GI, renal and reproductive toxicity, they have failed, with a possible exception in the case of celecoxib (see Celebrex product information, section 5.3), to indicate an increased risk of thromboembolic events related to application of selective COX-2 inhibitors in laboratory animals.

This may be related to the fact that COX-2 apparently attains significant (patho)physiological relevance only in animals with existing or developing CV disease, where its expression may be

strongly induced following for example ischaemic periods [e.g. in the myocardium (20)] or during atherogenesis (21, 22). Since safety pharmacology and toxicological studies were performed with primarily healthy animals, the molecular target (i.e. COX-2) may have been absent or not of (patho)physiological relevance in these studies. Therefore, the question arises whether future non-clinical assessment of selective COX-2 inhibitors

should consider the use of specific pathophysiological animal models for characterization of a coxib-associated CV risk.

The use of pathophysiological animal models is well established for characterisation of the pharmacodynamic properties of coxibs. Since their analgetic, antipyretic and anti-inflammatory properties cannot be assessed in healthy animals, specific pain, fever and inflammatory models have been used in non-clinical testing. The relevance of these animal models for human use has been established by a long experience with the conventional NSAIDs (23, 24).

While non-clinical data about a variety of adverse CV effects are meanwhile available for selective COX-2 inhibitors (some examples are given below), the relevance of these data for therapeutic use of coxibs in humans has not been firmly established till now:

- Effects on thrombosis and atherogenesis: In principle, non-clinical experiments supported the hypothesis that prostacyclin is important for these processes. Complete deletion of prostacyclin effects, e.g. in IP-receptor knockout mice, resulted in increased platelet activation (25), increased incidence of thrombosis following vascular injury (26), increased neointimal hyperplasia and increased atherosclerotic lesion area (27). Opposite effects were observed in TP-receptor knockout mice (25). Furthermore, enhancement of prostacyclin synthesis by gene transfer decreased intimal hyperplasia after vascular injury (28). However, it remains to be established whether the degree of inhibition of vascular endothelial prostacyclin synthesis achieved by therapeutic doses of coxibs (29, 30) is sufficient to elicit similar symptoms. In this respect, recent results obtained with mice in which just one copy of the IP-receptor was deleted (IP^{+/-}-mice) suggest adverse CV consequences also in the case of incomplete inhibition of prostacyclin effects (31).
- In several animal species, an inhibition of the anti-thrombotic activity of ASA by selective COX-2 inhibitors has been shown in models of induced thrombosis (32–34). Since, as deduced from *ex vivo* data, a direct inhibition of the anti-platelet effects of ASA by therapeutic doses of coxibs in humans is unlikely (35–37), the relevance of these data for use of coxibs in humans is currently unclear.
- Effects on MI/late phase of myocardial ischaemic preconditioning: There is evidence that selective COX-2 inhibitors impair the late phase of myocardial ischaemic preconditioning (LPMIP) and thereby render the heart more susceptible to ischaemic tissue damage and MI in animal experiments (20, 38). Since LPMIP may be of physiological relevance in humans as well (39, 40), these data raise concern about adverse effects of selective COX-2 inhibitors on the ischaemic human heart, e.g. in patients with coronary heart disease. However, an inhibition of the LPMIP would also be expected for conventional NSAIDs and is therefore as a single factor not sufficient to explain differences in CV adverse profile of coxibs and conventional NSAIDs.
- Effects on angiogenesis: Selective COX-2 inhibitors have been shown to impair angiogenesis, e.g. in association with cancer growth, gastric ulcer healing and corneal angiogenesis (41–43). However, it remains to be established whether similar inhibitory effects on angiogenesis in other tissues

exist and, in particular, whether protective angiogenic mechanisms operating in the myocardium of patients with ischaemic heart disease are impaired by selective COX-2 inhibitors.

In summary, the available non-clinical data raise concern about the CV safety of selective COX-2 inhibitors and suggest that the heart could be a particular target organ, since it could be affected in principle by both direct (local thrombus formation, vasoconstriction, stimulation of atherogenesis, impairment of LPMIP, impairment of angiogenesis) and indirect (increase in blood pressure/blood volume) mechanisms. Concerning potential long-term effects on atherogenesis and angiogenesis, the available data suggest that the full spectrum of adverse CV effects of coxibs may only become evident after long-term treatment.

Retrospectively, the clinical coxib data have confirmed these concerns. An increased MI rate was observed in coxib-treated patients and the risk appeared to be higher in patients with a history of ischaemic heart disease. Furthermore, CV toxicity was revealed in particular after long-term treatment, like e.g. in the APPROVe (5) and the APC study (8).

Nevertheless, for the prospective use of alternative non-clinical models for prediction of adverse CV effects of coxibs in humans during regulatory assessment, specific data are still required. A detailed look at the available non-clinical data shows that many studies have been designed to assess principal consequences of COX-2 inhibition but that full dose-response curves, assessment of the relative amount of COX-1 versus COX-2 inhibition and comparisons to conventional NSAIDs are just in some cases available. Therefore, in the ideal case, alternative non-clinical test systems should be validated comparing several dose levels of the coxib with a conventional NSAID in a well-defined pathophysiological model with probable relevance for human use. Furthermore, the evaluation should include toxicokinetic measurements to allow for an estimation of safety factors for human use based on a comparison of systemic exposure.

Clinical and epidemiological aspects

Several factors contributed to difficulties in assessment of CV safety of coxibs in clinical studies. For example, the risk for induction of thromboembolic events appears to be related to the 'basal' prothrombotic risk of the patient population studied. In patients with a high intrinsic thrombotic risk, as e.g. in CAGB patients, prothrombotic effects of coxibs (parecoxib, valdecoxib) were revealed within several days of treatment (10–12). As exemplified by the adverse CV effects of rofecoxib in the VIGOR study, thromboembolic effects may also be detected early during therapy of RA patients, which also appear to have an increased intrinsic basal thromboembolic risk (44). On the other hand, in patients with colon polyps, which do not appear to be at a high basal intrinsic thromboembolic risk, it took longer until thromboembolic effects of rofecoxib became detectable (APPROVe study). Of course, other factors may have contributed to the observed differences in time course and degree of prothrombotic effects, as for example the applied dose (i.e. rofecoxib 50 mg/day in VIGOR versus 25 mg/day in APPROVe) or the comparator used (naproxen-treated patients in VIGOR versus placebo-treated patients in APPROVe).

Finally, the chosen clinical CV endpoint may have influence on study interpretation. In several of the coxib 'outcome studies' the Antiplatelet Trialists' Collaboration (APTC) endpoint was selected as primary clinical CV safety endpoint. The APTC endpoint is a composite endpoint, summarising such different events as death from CV causes, non-fatal MI and ischaemic as well as haemorrhagic non-fatal stroke (45). While this is not a problem in placebo-controlled studies, it may complicate study interpretation in coxib studies using conventional NSAIDs as active comparators. For example, while the coxib may increase the rate of thromboembolic events (MI, ischaemic stroke), certain NSAIDs may increase the rate of haemorrhagic stroke (46). Therefore, while the resulting APTC endpoint may be similar, the spectrum of underlying adverse CV events may be significantly different between a coxib and a conventional NSAID, but this difference may remain unrecognised if the APTC is the only clinical study endpoint used. In addition, even for the endpoint MI, differences in definition exist between the different coxib studies. For example, while MI was defined in the VIGOR or APPROVe study as 'clinical' MI, in the TARGET study 'clinical' and 'silent' MI (the latter detected by electrocardiogram) were evaluated.

When first authorized, there were insufficient data showing a benefit of coxibs in long-term treatment of RA and OA patients compared to conventional NSAIDs. Moreover, knowledge of tolerability under normal use, i.e. outside clinical studies, was limited as with nearly all new chemical entities introduced in broad medical practice. Therefore, large clinical trials have been conducted post-approval, especially looking at GI tolerability (see Table 1). Based on the post-approval experience gained with the coxibs and other medicinal products during the last years, in the EU the so-called 'Review 2001' (47) came to the conclusion that in the future more emphasis should be placed on the collection of pharmacovigilance data and the prospective establishment of proper risk management systems. Meanwhile, these requests have been included in European drug laws (Directive 2001/83/EC of the European Parliament as amended) and regulatory guidelines [e.g. 'Note for guidance on planning pharmacovigilance activities' (CPMP/ICH/5716/03) and 'Guideline on risk management systems for medicinal products for human use' (EMA/CHMP/96268/2005)] and constitute an integral part of the standard drug approval process in the EU (48). It is now required to submit a detailed subscription of the pharmacovigilance and, where appropriate, risk-management system with the application for MA. Based on a specific pharmacovigilance specification of a medicinal product (e.g. identified pre-clinical safety concerns, missing preclinical data, adverse drug reactions in clinical trials, potential adverse drug reactions requiring further evaluation, data on special populations, etc.) a pharmacovigilance plan proposes the investigation of data relevant to the safety profile of a medicinal product to allow demonstration of safety as well as to identify possible harm (49, 50). Resting on the experience with the coxibs more extensive and earlier assessment of pharmacoepidemiologic data will be implemented in these pharmacovigilance plans. We believe that the implementation of these new risk management tools (51) will strengthen pharmacovigilance and results in more effective and balanced regulatory actions by regulators and industry.

Appendix to Table I: EMEA press releases

1: 22/10/2002 – EMEA/25175/02

EMEA public statement on parecoxib sodium (Dynastat/Rayzon/Xapit) – Risk of serious hypersensitivity and skin reactions:

Data description: Serious hypersensitivity and serious skin reactions have been observed with valdecoxib, some in patients with a history of allergic-type reactions to sulphonamides. Valdecoxib is the active metabolite of parecoxib sodium. It is therefore possible that such reactions may also occur with parecoxib sodium.

Regulatory actions: Urgent measures – Change of parecoxib product information (SPC): – Additional contraindication (SPC 4.3): hypersensitivity to sulphonamides; Additional warnings (SPC 4.4): in post marketing experience, hypersensitivity reactions including anaphylaxis, angioedema and serious skin reactions including erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in association with valdecoxib. Additional adverse effects (SPC 4.8): in rare cases – erythema multiforme, exfoliative dermatitis, Stevens-Johnson-syndrome, toxic epidermal necrolysis

2: 30/04/2004 – EMEA/CPMP/1747–1749/04

CPMP opinion following an Article 31 referral for all medicinal products (MP) containing celecoxib, etoricoxib, parecoxib, rofecoxib or valdecoxib:

Overall conclusions: The CPMP considered that the benefit/risk balance of MP containing the mentioned coxibs remains favourable and recommended the maintenance of their MA.

Scientific conclusions: Efficacy issues: Efficacy in the claimed indications was confirmed. Safety issues: – GI toxicity: Available data on perforations, ulcers and bleeds (PUBs) indicated that significant and consistent benefit of coxibs compared with conventional NSAIDs has not been demonstrated. It is unknown whether the GI toxicity profile of coxibs in association with ASA is inferior to conventional NSAIDs but there is no evidence to suggest it would be superior. – CV toxicity: The available pre-clinical data raised concern about CV safety, in particular MI, however, conflicting results have often been obtained. The difference in antiplatelet activity between some COX-1 inhibiting NSAIDs and COX-2 selective inhibitors may be of clinical relevance in patients at risk of thromboembolic reactions. In contrast to COX-1 inhibiting NSAIDs, coxibs have no antiplatelet effects in therapeutic doses. With respect to CV risk it can be concluded that there may be a safety disadvantage of coxibs compared to conventional NSAIDs. – Hypersensitivity and serious skin reactions: Single cases of serious cutaneous adverse reactions, i.e. Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported for coxibs. The absolute numbers and estimation of frequency suggest that these reactions occur very rarely.

Product information: Contraindication (SPC section 4.3): No new contraindications should be added in any of the concerned SPCs – Warnings (SPC section 4.4): Harmonized wording which should be included in the SPC of all selective COX-2 inhibitors – see Table 2.

3: 06/10/2004 – EMEA/97949/2004

EMEA statement following withdrawal of Vioxx (rofecoxib)

Data description: Worldwide withdrawal of Vioxx (rofecoxib) based on an increased risk of confirmed serious thrombotic events (including MI and stroke) following long-term use (>18 months) in patients with intestinal polyps.

Information to prescribers and patients: Patients on Vioxx should be reviewed and alternative treatment considered. When switching to another COX-2 inhibitor, the revised SPC, especially regarding the warnings and precautions in patients with a history of CV disease, should be carefully followed.

4: 22/10/2004 – EMEA/117908/2004

EMEA to review COX-2 inhibitors

Data description: The European Commission asked the EMEA to conduct a review of the CV safety (thrombotic and cardio-renal events) of coxibs.

Regulatory actions: The objective is to assess whether there is a need to make changes to existing MA and whether additional studies are needed.

5: 15/12/2004 – EMEA/204802/2004

EMEA public statement on valdecoxib (Bextra/Valdyn) and parecoxib sodium (Dynastat/Rayzon) – CV risks in coronary artery bypass graft (CABG) surgery and serious adverse skin reactions

Data description: (i) CV safety – higher rate of serious CV thromboembolic events in two CABG studies after parecoxib/valdecoxib treatment compared with placebo. (ii) Serious skin reactions – rate appears to be higher for valdecoxib than for other selective COX-2 inhibitors, patients appear to be at highest risk early in the course of therapy.

Regulatory actions: SPC changes – (i) Contraindication of parecoxib/valdecoxib in patients after CABG surgery. – (ii) Additional warning concerning serious skin reactions – therapy should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

6: 17/12/2004 – EMEA/205831/2004

EMEA statement on celecoxib

Data description: (i) APC study shows an apparently dose-related increased risk of major fatal and non-fatal CV events (i.e. MI and stroke) in patients taking celecoxib (average treatment duration 33 months) compared with patients taking placebo. Trial was stopped. (ii) A second trial (PreSAP) does not appear to confirm this risk. However, trial was also stopped.

Regulatory actions: EMEA requested results of both studies for review within the context of the coxib-referral.

7: 22/12/2004 – EMEA/212271/2004

Updated statement from EMEA on celecoxib

Data description: EMEA received summary data on APC and PreSAP. Regulatory actions: EMEA decided to accelerate the ongoing coxib-referral. Pending the outcome of the referral, national authorities in the Member states have made recommendations for the use of COX-2 inhibitors.

8: 20/01/2005 – EMEA/23547/2005

Update from the EMEA on COX-2 inhibitors

Data description: Hearings were held with MA holders.

Regulatory actions: Further data on APC and PreSAP were requested. Pfizer agreed not to launch Onsenal in EU pending finalization of the assessment.

9: 17/02/2005 – EMEA/62838/2005

EMEA announces regulatory action on COX-2 inhibitors

Data description: The CHMP concluded that the available data show an increased risk of CV adverse effects for coxibs as a class and an association between duration and dose of intake and risk. Since more research is needed, ongoing CV trials should continue as planned.

Regulatory actions: (i) Contraindications: all coxibs – patients with ischemic heart disease, for etoricoxib: uncontrolled hypertension (ii) warnings for patients with risk factors for heart disease.

10: 07/04/2005 – EMEA/121637/2005

EMEA statement on the suspension of use of Bextra

Regulatory actions: Following discussions with the EMEA, Pfizer agreed to the suspension of use of Bextra (valdecoxib) in Europe as an interim measure pending finalisation of the coxib referral.

11: 27/06/2005 – EMEA/207766/2005

EMEA concludes action on COX-2 inhibitors

Data description and regulatory actions: see manuscript text concerning second EU coxib referral and Table 2.

12: 27/06/2005 – EMEA/210745/2005 corr

Questions and answers on COX-2 inhibition

Answer document to frequently asked questions about coxibs.

13: 02/08/2005 – EMEA/247323/2005

EMEA Press release on non-selective NSAIDs

Data description: Following a request from the European Commission in June 2005 the CHMP assessed available data on CV safety of non-selective NSAIDs.

Regulatory actions: Concerning thrombotic risk no immediate regulatory actions are recommended. However, the lowest effective dose for the shortest time necessary to control symptoms should be used. Data on GI safety and serious skin reactions are still under review.

14: 02/08/2005 – EMEA/250423/2005

Questions and answers on non-selective NSAIDs

Answer document to frequently asked questions about non-selective NSAIDs.

15: 11/08/2005 – EMEA/265602/2005

Public statement on Valdyne (valdecoxib). Withdrawal of the MA in the EU

Regulatory actions: in agreement with the MA holder, the European Commission adopted the decision to withdraw the MA of valdyne (valdecoxib) in the EU.

16: 17/10/2005 – EMEA/298964/2005

EMEA update on non-selective NSAIDs

Data description: There are no new safety concerns regarding CV and GI safety and serious skin reactions with non-selective NSAIDs

Regulatory actions: Product informations should be made consistent across the EU by including a set of key elements (see Table 3) that should be implemented at the national level.

17: 17/10/2005 – EMEA/CHMP/343456/2005

Key elements for the SPCs of non-selective NSAIDs as adopted by the CHMP during its meeting in October 2005.

See Table 3.

18: 17/10/2005 – EMEA/300095/2005

Questions and answers on the EMEA review of CV and GI safety and serious skin reactions with non-selective NSAIDs

Answer document to frequently asked questions about non-selective NSAIDs.

19: 27/10/2005 – EMEA/358234/2005

EMEA public statement on the suspension of the MA for Bextra (valdecoxib) in the EU

Data description: the European Commission issued a decision to suspend the MA of Bextra (valdecoxib), whereby confirming the decision by the CHMP in June 2005.

20: 09/11/2005 – EMEA/CVMP/108858/2005-Rev.1

COX-2 inhibitors in veterinary medicine

Data description: The CVMP assessed the effects of coxibs and of conventional NSAIDs for food producing animals and for companion animals.

Data description: No immediate regulatory action was considered necessary.

21: 28/11/2005 – EMEA/CHMP/323166–324317–324333/2005

CHMP opinion following an Article 31 referral for all medicinal products containing celecoxib, etoricoxib, lumiracoxib, parecoxib, and valdecoxib

Regulatory actions: The European Commission confirmed the CHMP opinion of June 23, 2005 (see EMEA press releases 11+12).

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