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Assessment Report for Celecoxib for the reduction of the number of adenomatous intestinal polyps in familial adenomatous polyposis, as an adjunct to surgery and further endoscopic surveillance

Review under Article 5(3) of **Regulation (EC) No 726/2004**

Procedure no: EMEA/H/A-5(3)/1303

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.



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1. Background information on the procedure

1.1. Request for CHMP opinion

On 28 March 2011, the European Commission requested the CHMP to draw up an opinion, on the basis of the information currently available, on the use of celecoxib for the reduction of the number of adenomatous intestinal polyps in familial adenomatous polyposis (FAP), as an adjunct to surgery and further endoscopic surveillance. This opinion was requested under Article 5(3) of Regulation 726/2004.

One celecoxib-containing product has been previously approved in the European Union for this rare indication. Onsenal (celecoxib) received the orphan designation for FAP patients in 2001, and was granted a marketing authorisation under exceptional circumstances by the European Commission in 2003. This marketing authorisation was subject to specific obligations under which the marketing authorisation holder (MAH) was required to generate and submit further data on the efficacy and safety of the product.

In March 2011, the MAH informed the Agency of its decision to voluntarily withdraw the marketing authorisation for the product. The decision was justified on the basis of slow enrolment in a clinical trial, which caused the MAH to be unable to fulfill the specific obligations associated to the marketing authorisation. At the time of the withdrawal, Onsenal was undergoing the 8th annual reassessment and, on the basis of the documentation submitted, the CHMP was of the view that the specific obligation necessary to maintain the marketing authorisation had not been fulfilled.

On 28 March 2011 the European Commission issued a decision withdrawing the marketing authorisation for the product. Following the withdrawal of the marketing authorisation for Onsenal, there is currently no medicinal product approved in the EU for the reduction of the number of adenomatous intestinal polyps in FAP patients. However, celecoxib-containing products continue to be approved and marketed throughout the European Union for other therapeutic indications, and it is possible that these are used off-label for the reduction of the number of adenomatous intestinal polyps in FAP patients. The European Commission therefore considered that it would be important from a public health standpoint that the CHMP adopts an opinion on the matter.

2. Scientific discussion

2.1. Introduction

Celecoxib is an orally selective cyclooxygenase-2 (COX-2) inhibitor. Elevated levels of COX-2 are found in many pre-malignant lesions (such as adenomatous colorectal polyps) and epithelial cancers.

Familial Adenomatous Polyposis (FAP) is a genetic disease with prevalence between 0.3 to 1 in 10,000 people within the EU, resulting from an autosomal dominant genetic alteration of a tumour suppressor gene, the adenomatous polyposis coli (APC) gene. Polyps with the APC mutation overexpress COX-2 enzyme and, if left untreated, continue to form and enlarge in the colon or rectum resulting in essentially a 100% risk of developing colorectal cancer. The current standard therapy in the EU is endoscopic surveillance and surgery.

2.2. Clinical efficacy

Study IQ4-99-06-001

The effect of Celecoxib in reducing the number of adenomatous colorectal polyps was evaluated in a single randomized double-blind, three arm, placebo-controlled study (IQ4-99-06-001) involving 83 patients with FAP.

The study was conducted at two sites, one in the UK and one in US. Seventy seven patients with lower gastro-intestinal tract disease plus 6 patients with exclusively duodenal lesions were enrolled. The study population included 58 patients with a prior subtotal or total colectomy and 25 patients with an intact colon. Thirteen patients had the attenuated FAP phenotype.

One area in the rectum and up to four areas in the colon were identified at baseline for specific follow-up. Polyps were counted at baseline and following six months of treatment.

The mean reduction in the number of colorectal polyps was 28% for Celecoxib 400 mg BID, 12% for Celecoxib 100 mg BID and 5% for placebo. The reduction in polyps observed with Celecoxib 400 mg BID was statistically superior to placebo at the six-month time point ($p=0.003$).

Figure 1 shows the observed reduction in number of polyps, reflecting the inter-individual variability in drug effect.

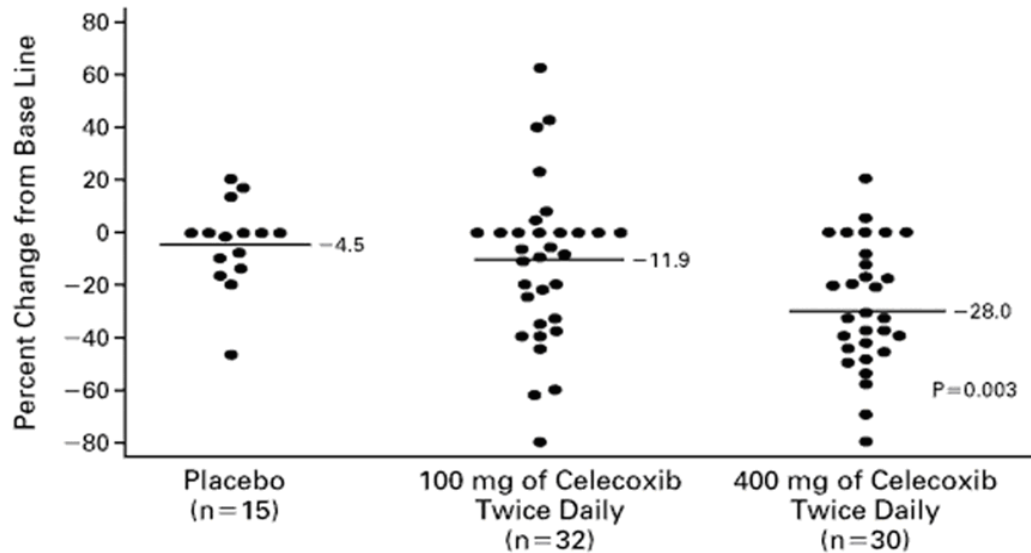


Figure 1 Percent change from baseline in the number of colorectal polyps in 77 patients with FAP who were treated with placebo or celecoxib (100 mg twice a day or 400 mg twice a day) for six months.

Quality of life was determined at baseline, at month 3 and 6 or at early termination using the SF-36 health survey. No statistically significant improvement as compared to placebo was observed.

CHIP (Children's International Polyposis) study

The CHIP study (protocol A3191193) is a phase III, double-blind, randomised, placebo-controlled, multi-centre trial in subjects with FAP. The study was designed to compare efficacy and safety of celecoxib versus placebo over a 5-year treatment period.

A planned total of 200 subjects with non-attenuated FAP genotypes (aged 10 to 17 years) who have no polyps or have <20 polyps (>20 mm in size) at baseline removed via colonoscopy, were to be randomised 1:1 to treatment with either celecoxib (11 to 16 mg/kg/day) or placebo for a 5-year period.

The primary endpoint of the study is time to either colorectal malignancy or the appearance of >20 polyps (>2 mm in size), as assessed annually using colonoscopy.

According to statistical assumptions, a total of 152 events will be needed to declare celecoxib treatment superior to placebo ($HR=1.576$) at a significance level of 0.05 with 80% power. Interim efficacy analyses will occur at increments of approximately 30 primary endpoint events.

The study was initiated in September 2006 and is currently ongoing. Table 1 summarises numbers and rates of randomisation in the CHIP trial incrementally from July 2008 through November 2010.

Table 1 Subject Randomization in the CHIP Trial, as of 11 November 2010

Date	Number of Sites Recruiting	Number of Subjects Randomized		Monthly Rate of Randomization for the Increment
		Actual Total at Each Date	Incremental Increase (period)	
July 2008		1		
July 2009	15	22	22 (12 months)	1.8 subjects/month
November 2009		29		
March 2010		38		
July 2010	18	41	19 (12 months)	1.6 subjects/month
November 2010	23¹	50	9 (3.3 months)	2.7 subjects/month

¹ A total of 4 additional investigational sites were either in the process of ethics board approval as of 11 November 2010, or have received approval and are in the process of identifying potential subjects for screening.

Due to extremely slow recruitment, no data from the CHIP trial is yet available. The expected date for conclusion of the study has been shifted from 2013 to 2019. This continuous delay has led to the withdrawal of the FAP indication in the USA.

Published literature

Recently Lynch PM et al. (Am J Gastroenterol. 2010) published results from a small study aimed to investigate the short-term (3 months) safety and preliminary efficacy of celecoxib in children with APC gene mutations and/or adenomas with a family history of FAP.

The study was a phase I, dose-escalation trial, with three successive cohorts of six children aged 10-14 years. Colonoscopy was performed at baseline and month 3. Adherence and adverse event monitoring was conducted at 2-week intervals during drug administration. Safety profile, difference in number, and percent change in colorectal polyps were compared among the four treatments (placebo and the three dose-escalation groups).

Eighteen subjects completed drug dosing and both colonoscopies. Median age was 12.3 years (56% female). Median polyp count at baseline was 31. There was a 39.1% increase in the number of polyps in placebo subjects at month 3, whereas in the highest dose celecoxib group (16 mg/kg/day) a 44.2% reduction was seen (P=0.01).

Table 2 Dosing of patients within each of the three cohorts

	Cohort 1, n=6 (2:1 drug: placebo)	Cohort 2, n=6 (2:1 drug: placebo)	Cohort 3, n=6 (2:1 drug: placebo)
Body weight	Celecoxib dose 4 mg/kg	Celecoxib dose 8 mg/kg	Celecoxib dose 16 mg/kg
25.0–37.5 kg	50 mg BID	100 mg BID	200 mg BID
37.6–50.0 kg	100 mg BID	150 mg BID	300 mg BID
>50.0 kg	100 mg BID	200 mg BID	400 mg BID

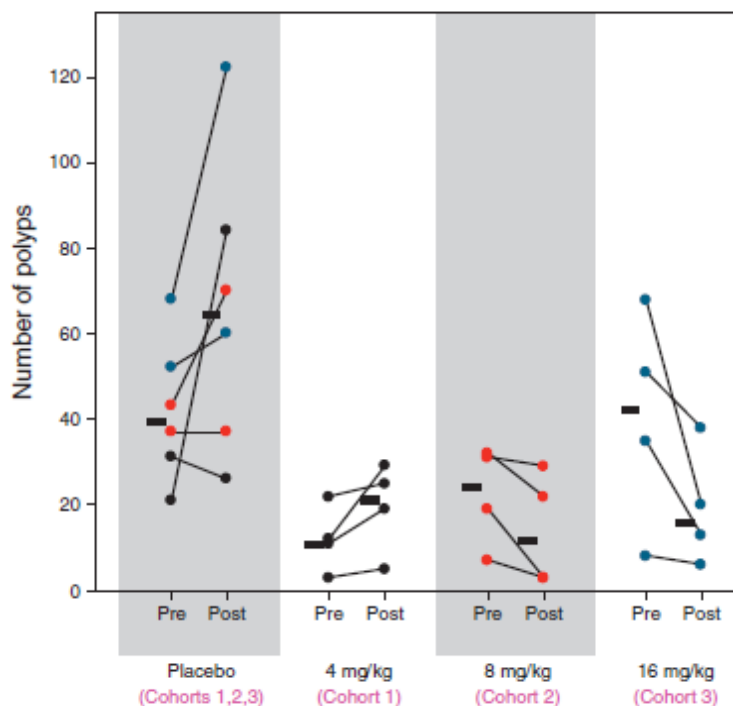


Figure 2 Celecoxib dose – response relationship among pediatric patients with familial adenomatous polyposis. The number of polyps at baseline (pre) and after 3 months of treatment (post) for the placebo ($n = 4$) group and patients treated with 4 mg/kg/day ($n = 4$), 8 mg/kg/day ($n = 4$), and 16 mg/kg/day ($n = 4$). Median number of polyps (denoted by horizontal bars) increased for children receiving placebo or 4 mg/kg/day celecoxib and decreased for children who received 8 mg/kg/day or 16 mg/kg/day celecoxib.

Discussion on efficacy

The IQ4-99-06-001 trial continues to be the main source of efficacy data for celecoxib in the FAP indication. A number of limitations can be identified in this study, and have not been clarified by further studies.

The limited sample size ($n=83$) raises the issue of whether the study population is representative of the general FAP population.

A 28% change from baseline was observed in the primary efficacy endpoint (number of colorectal polyps) for celecoxib 400 mg twice a day. However this change was lower than the prespecified 40% difference for which the study was powered and which was considered a clinically relevant difference. Even though a small reduction in polyps number might possibly be translated into an absolute reduction of the risk of developing cancer, the impact on the clinical approach to the disease is unclear and therefore it is also unclear whether or not the findings are clinically relevant. The effect of celecoxib treatment on the risk of gastrointestinal cancer and on the need for FAP related surgeries was not assessed, and no statistically significant difference was observed in quality of life parameters.

Furthermore, as the IQ4-99-06-001 study was limited to a 6-month period, it is also unclear whether any absolute improvement in terms of reduction of number of polyps is maintained in long-term therapy.

The CHIP trial was designed to provide long term efficacy and safety data on celecoxib in the reduction of number of polyps in FAP patients. As no data has been generated to date, no conclusions can be drawn. In view of the recent withdrawal of the marketing authorisations for celecoxib in FAP patients in Europe, the United States and Canada, it seems likely that the enrolment problems observed with the CHIP trial will persist.

A further study recently published in the Am J Gastroenterol. does not provide relevant additional information considering the small number of patients included ($n=6$ at the high dose) and the short duration (3 months).

The methodological limitations and the weakness of the results of the IQ4-99-06-001 study have not been solved with further confirmatory studies. Thus, the clinical benefit of celecoxib as a chemopreventive agent in the FAP indication is, at present, not sufficiently demonstrated.

2.3. Clinical safety

Study IQ4-99-06-001

The most commonly reported adverse events were diarrhoea, dyspepsia, fatigue, blood per rectum (rectal spotting), upper respiratory infection and rash.

Table 3 Most commonly reported adverse events in IQ4-99-06-001 study

Adverse event	Placebo (n=17)	Celecoxib 100 mg BID (n=34)	Celecoxib 400 mg BID (n=32)
Diarrhea	6 (35.3%)	11 (32.4%)	14 (43.8%)
Dyspepsia*	5 (29.4%)	9 (26.5%)	11 (34.4%)
Fatigue	8 (47.1%)	6 (17.6%)	10 (31.3%)
Blood Per Rectum	2 (11.8%)	3 (8.8%)	10 (31.3%)
URTI	6 (35.3%)	13 (38.2%)	9 (28.1%)
Rash	3 (17.6%)	1 (2.9%)	9 (28.1%)

*All patients with negative endoscopy at end of study

The types of side effects of celecoxib reported in the FAP population were similar to those observed in the arthritis population. Intestinal surgical anastomotic ulceration was the only adverse event reported by celecoxib-treated patients in the FAP trial that was not reported in the arthritis studies. This was observed in 3 of 58 patients who had prior intestinal surgery before entering the FAP study.

The study was inadequately powered to assess any difference in serious adverse events between celecoxib and placebo (n=83).

COX-2 inhibitors referrals

Two major safety reviews of the COX-2 inhibitors (including celecoxib) at European level were completed as follows:

- On 20 November 2003, the CHMP concluded a **referral under Article 31** to review the **gastrointestinal and cardiovascular safety**, as well as serious hypersensitivity and serious skin reactions of nationally authorised medicinal products containing celecoxib, etoricoxib, parecoxib, rofecoxib or valdecoxib. Following the assessment of the available data, the CHMP recommended the update of the product information for celecoxib-containing products to include warnings on skin and hypersensitivity disorders, gastrointestinal and cardiovascular risk.

- On 23 June 2005, the CHMP concluded a **referral under Article 31** concerning the **cardiovascular safety and serious skin reactions** of nationally authorised products containing celecoxib, etoricoxib, and lumiracoxib and its **review under Article 18** concerning the **cardiovascular safety and serious skin reactions** of the centrally authorised products containing celecoxib, parecoxib or valdecoxib. The CHMP concluded that there was an increased risk of cardiovascular adverse reactions associated with celecoxib and with COX-2 inhibitors as a class, and agreed that there was an association between duration and dose of intake and the probability of suffering such reactions. The review also concluded that celecoxib is associated with very rare occurrence of serious skin reactions, as evidenced in clinical studies and postmarketing surveillance.

The CHMP was of the opinion that the benefit/risk balance of celecoxib in the FAP indication remained positive and that the MA granted under exceptional circumstances, i.e. subject to specific obligations to generate and submit further data on the efficacy and safety of the product, should be maintained following changes to the product information. It was also recommended that cardiovascular safety and serious skin reactions should be continuously and carefully monitored and assessed.

Periodic Safety Update Reports

During the period covered by the latest PSUR for the FAP indication (1 November 2009-31 October 2010), a total of eight medically confirmed cases (containing 16 events) fulfilled criteria for inclusion in this one-year safety update report. There was one case reporting a fatal outcome, which was associated with diarrhea and sepsis. There was also one case that involved a gastrointestinal hemorrhage and one case that involved a non-SCAR cutaneous event that met criteria to be considered serious. Only three system organ classes (Gastrointestinal disorders, Investigations, and Skin and subcutaneous disorders) involved more than one event and only one event (diarrhea) was reported in more than one case.

The latest celecoxib PSUR for all indications (including oncology) included a specific review and discussion on cases reporting cardiovascular events, cerebrovascular events, gastrointestinal hemorrhage, hepatic failure, thromboembolic events, and serious cutaneous events, and severe cutaneous adverse reactions (SCARs).

CHIP (Children's International Polyposis) study

As of 02 November 2010, adverse event data were available for 40 subjects in the CHIP trial. Of these 40 subjects, a total of 23 subjects had adverse events (serious and non serious adverse events considered together). There were no deaths, and there were 2 serious adverse events (abdominal pain and pleural effusion). Neither of these serious adverse events was considered related to study medication by the investigator.

Consistent with the known safety profile for celecoxib and the expected background incidence of particular adverse events in FAP patients, 10-17 years of age at baseline, the most common adverse events to date have been those coding to the gastrointestinal disorders system organ class (vomiting, nausea, etc - 35% of subjects) and to the infections and infestations SOC (gastroenteritis, nasopharyngitis, pyrexia, etc - 30% of subjects). Among other particular adverse events of interest for celecoxib, there were no subjects with cardiovascular thromboembolic adverse events, one subject with hypertension, and no subjects with severe cutaneous adverse reactions (SCAR, defined as Stevens-Johnson syndrome, toxic epidermal necrolysis, and/or erythema multiforme).

APC and PreSAP trial

Data from large long-term placebo-controlled trials of celecoxib in the prevention of adenomatous colonic polyps (a non-approved indication) suggest a dose-related increase in risk of cardiovascular death, nonfatal MI, or stroke.

In the adenomatous polyp prevention trial (APC trial), 2035 patients were randomly assigned to either celecoxib (400 mg twice daily or 200 mg twice daily) or placebo. At the mean follow up of 33 months, the analysis of cardiovascular safety reported 18 events among 683 subjects (RR 2.6, 95% CI 1.1-6.1) treated with celecoxib 200 mg BID and 23 events among 669 subjects (RR 3.4, 95% CI 1.5-7.9) who received celecoxib 400 mg BID. Seven cardiovascular events (nonfatal MI, stroke, heart failure, or cardiovascular death) were reported on 676 patients in the placebo arm.

As a result of the finding of a dose related increased risk of cardiovascular events and death due to cardiovascular causes, the DSMB (data-safety monitoring board) discontinued the APC trial.

A long-term trial in patients with previous colonic polyps (PreSAP trial) randomly assigned 1561 subjects to either celecoxib (400 mg daily) or placebo. Although the increased risk in the PreSAP trial was not statistically significant (2.5 versus 1.9 percent, RR 1.30, 95% CI 0.65-2.62), an analysis of data on cardiovascular events from the two placebo-controlled adenoma prevention trials (APC and PreSAP trials) concluded that there was an increase in serious cardiovascular events that may be dose related.

For APC and PreSAP combined, 83 patients experienced cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or heart failure. The hazard ratio for this pre-specified composite end point was 2.6 (95% confidence interval [CI], 1.1 to 6.1) in patients taking 200 mg twice daily, **3.4 (95% CI, 1.5 to 7.9) in patients taking 400 mg twice daily in APC**, and 1.3 (95% CI, 0.6 to 2.6) in patients taking 400 mg once daily in PreSAP (P for heterogeneity = 0.13 comparing the combined

doses in APC with the dose in PreSAP). The overall hazard ratio for this composite end point was 1.9 (95% CI, 1.1 to 3.1).

Both dose groups in APC showed significant systolic blood pressure elevations at 1 and 3 years (200 mg twice daily: 1 year, 2.0 mm Hg; 3 years, 2.6 mm Hg; 400 mg twice daily: 1 year, 2.9 mm Hg; 3 years, 5.2 mm Hg).

Published literature

The cardiovascular risk associated with long-term exposure and high-dose celecoxib (i.e., 800 mg daily as recommended in FAP patients) has been addressed in COX inhibitors referral procedures and confirmed by meta-analyses (Kearney et al. BMJ 2006; Solomon et al. Circulation 2008, Treller et al., BMJ 2011).

As shown in the meta-analysis by Solomon et al., the results are consistent with and strengthen the preliminarily evidence of a dose-related cardiovascular toxicity of celecoxib.

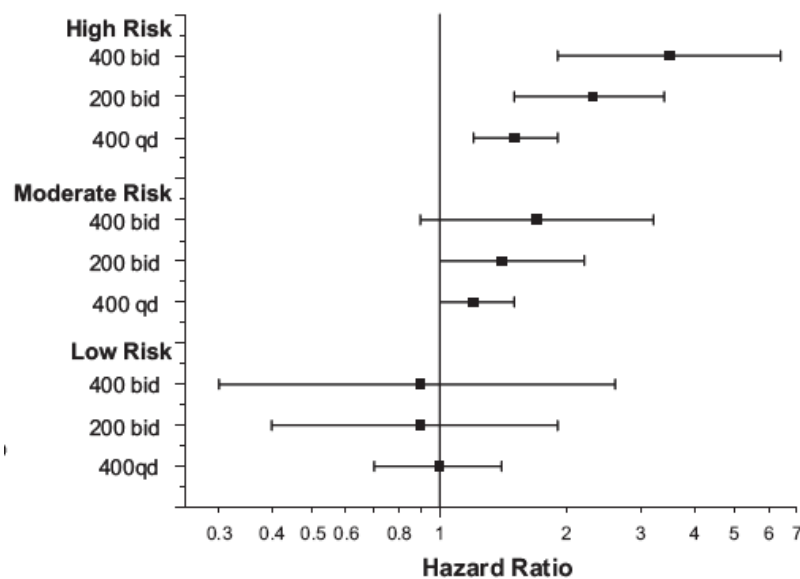


Figure 3 Relationship between celecoxib dose, baseline CV risk and combined outcome of CV death, myocardial infarction, stroke, heart failure, or thromboembolic event

Source: Solomon et al. Circulation, April 22, 2008

Findings from the latest meta-analysis (Treller et al., BMJ 2011) confirmed that celecoxib use is associated with a dose-dependent risk of cardiovascular events similar to most non-selective NSAIDs.

The risk of CV events associated with celecoxib relative to other NSAIDs was addressed in a 2011 network meta-analysis of large randomized trials involving celecoxib, rofecoxib, lumiracoxib, etoricoxib, ibuprofen, diclofenac, and naproxen; the risk of myocardial infarction with celecoxib compared with placebo (RR, 1.35, 95% CI, 0.71-2.72) was lower than that for rofecoxib (RR 2.12, 95% CI 1.26-3.56) or ibuprofen (RR 1.61, 95% CI 0.50-5.77), but greater than naproxen (RR 0.82, 95% CI 0.37-1.67), which had the most favourable cardiovascular risk profile.

Additional data from studies in other indications

In the CLASS study, celecoxib 400 mg BID was associated with an annual rate of upper GI complications of 8 per 1,000 patients that was not significantly lower than the rate of complications in NSAID-treated patients (*Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study - JAMA 2000; 284: 1247-1255*).

The SUCCESS-I study (*Celecoxib Versus Naproxen and Diclofenac in Osteoarthritis Patients: SUCCESS-I Study*. The American Journal of Medicine 2006; 119(3) 255-266) included a total of 13,274 patients with osteoarthritis, 8,800 of whom were randomly assigned to celecoxib (100 or 200 mg twice daily for 12 weeks) and 4,394 of whom were assigned to diclofenac 50 mg or naproxen 500 mg twice daily for 12 weeks. Despite the two-fold larger size of the combined celecoxib groups as compared to the combined NSAID groups, the number of clinically significant ulcers was equal in the two groups (18 ulcers in each group). Only nine ulcer complications occurred in this study, seven in the combined NSAID group, and two in the combined celecoxib group ($p = 0.008$). The study was underpowered to detect a difference in cardiovascular events between the groups. However, there were 10 myocardial infarctions in the larger combined celecoxib group as compared to 1 in the two-fold smaller combined NSAID group (OR 0.2 for NSAID group, 95% CI 0.03-1.56).

Discussion on safety

The safety data on celecoxib adjunctive therapy in FAP patients are still very limited. The pivotal study for the FAP indication (IQ4-99-06-001) was inadequately powered to assess any difference in adverse events between celecoxib and placebo. Further data was expected to be collected in the CHIP trial, but the study has not progressed much in terms of recruitment so results are not expected to be available before 2019.

While the safety data of celecoxib as adjunctive therapy in FAP patients are still very limited, a considerable amount of data exists on the safety of celecoxib in other indications. This data points clearly to an increased risk of gastrointestinal and cardiovascular adverse events with increasing dose and exposure time.

These risks had been identified and assessed by CHMP in the past, leading to two major class safety reviews at European level. Based on the data available at the time, the Committee concluded that the benefit-risk balance of celecoxib remained positive provided adequate warnings on the risks be included in the product information. The Committee also recommended that the risks identified should be continuously monitored and assessed.

As further data becomes available and new meta-analyses are published, the increased cardiovascular and gastrointestinal risk associated to celecoxib is further confirmed. As the risk has been demonstrated to be dose- and exposure time-related, this is particularly relevant for FAP patients, who are exposed to higher doses and long-term treatment. The APC trial [HR = 3.4 (95% CI, 1.5 to 7.9) for patients taking 400 mg BID] represents perhaps the best estimation of the increased cardiovascular risk in the FAP population, as it was also conducted using long-term treatment with the same dose regimen studied in FAP.

2.4. Overall benefit/risk assessment

The IQ4-99-06-001 trial continues to be the main source of efficacy data for celecoxib in the FAP indication. The methodological limitations and weakness of the results has not been solved with further confirmatory studies. There is no evidence that celecoxib has an effect on the risk of gastrointestinal cancer and on the need for FAP related surgeries. Thus, the clinical benefit of celecoxib as a chemopreventive agent in the FAP indication is, at present, not sufficiently demonstrated.

On the other hand, more data on the safety of celecoxib has become available over time. This data strengthens the association between celecoxib and an increased risk of cardiovascular and gastrointestinal adverse events. The risk has been demonstrated to be dose- and exposure time-related, and is therefore of particular concern for FAP patients. It is recognised that the majority of FAP patients are relatively young and, in principle, less prone to develop cardiovascular-related adverse events. Nevertheless there are still FAP patients in older age groups (>50 years old), and it has to be kept in mind that an acute coronary event in younger patients is more severe than in an older patient as it is often associated with sudden death or severe left ventricular dysfunction.

A patients' organisation was consulted with regards to the use of celecoxib in FAP patients. The feedback provided confirmed that use in this indication has decreased over time due to the perception

that it is associated to an uncertain clinical benefit. Experience with celecoxib in the FAP indication does not seem to indicate benefit in terms of frequency of endoscopic/surgical interventions.

3. Overall conclusion

The CHMP considered the procedure under Article 5(3) of Regulation (EC) No 726/2004 on the use of celecoxib for the reduction of the number of adenomatous intestinal polyps in familial adenomatous polyposis, as an adjunct to surgery and further endoscopic surveillance, initiated by the European Commission.

Based on the overall available data on the efficacy and safety of celecoxib in the concerned indication, which is currently not approved in the EU, the CHMP is of the opinion that:

- there is uncertainty on the clinical benefit of treatment with celecoxib for the reduction of the number of adenomatous intestinal polyps in patients with familial adenomatous polyposis,
- celecoxib, at high doses and long-term use, as in the treatment of FAP patients, is associated with an increased risk of gastrointestinal and cardiovascular adverse events.

The Committee therefore concluded that, in view of the risks associated with celecoxib, the currently available evidence of efficacy is insufficient to support its use in the reduction of the number of adenomatous intestinal polyps in patients with familial adenomatous polyposis.