

**Public Assessment Report
for paediatric studies submitted in accordance
with Article 46 of Regulation (EC) No1901/2006, as
amended**

**Celebra / Celebrex / Solexa / Aclarex / Artilog /
Celecoxib Pfizer
(celecoxib)**

MT/W/0010/pdWS/001

Marketing Authorisation Holder: PFIZER

Rapporteur:	Malta
Finalisation procedure (day 120):	22/01/2016

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Celebra / Celebrex / Solexa / Aclarex / Artilog / Celecoxib Pfizer
INN (or common name) of the active substance(s):	Celecoxib
MAH:	PFIZER
Currently approved Indication(s)	Symptomatic relief in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis The decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's overall risks (see sections 4.3, 4.4).
Pharmaco-therapeutic group (ATC Code):	M01AH01
Pharmaceutical form(s) and strength(s):	Hard capsules for oral use: 100mg and 200mg

LIST OF ABBREVIATIONS

ABPM	Ambulatory blood pressure monitoring
ACR	American College of Rheumatology
AE	Adverse event
AS	ankylosing spondylitis
BP	blood pressure
BID	twice daily
CI	confidence interval
COX	cyclooxygenase
CSR	clinical study report
DBP	diastolic blood pressure
DMARD	disease-modifying anti-rheumatic drug
EU	European Union
FAP	familial adenomatous polyposis
FDA	Food and Drug Administration
GI	gastrointestinal
ILAR	International League of Associations for Rheumatology
JIA	juvenile idiopathic arthritis
JRA	juvenile rheumatoid arthritis
LS	least square
MAH	marketing authorisation holder
MITT	modified-intent-to-treat
NSAID	non-steroidal anti-inflammatory drug
OA	osteoarthritis
PMC	post-marketing commitment
PY	patient-year
RA	rheumatoid arthritis
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SINCERE	Safety in Idiopathic Arthritis: NSAIDs and Celebrex Evaluation Registry
SmPC	Summary of Product Characteristics
TEAE	treatment-emergent adverse event
US	United States
VAS	VISUAL ANALOGUE SCALE

I. EXECUTIVE SUMMARY

No SmPC and PL changes are proposed.

II. RECOMMENDATION

In connection with this Paediatric Work Sharing (PdWS) procedure according to Article 46 of the Paediatric Regulation (EC) 1901/2006 as amended, basing on a review of the paediatric data submitted by the MAH regarding the treatment of children with celecoxib, procedure number MT/ W / 0010 / pdWS /001, and basing on current literature regarding the safety of celecoxib, in this Public Assessment Report it is recommended that regarding celecoxib no SmPC and no PL changes are required.

III. INTRODUCTION

On the 10th June 2015, the MAH submitted a completed paediatric study report for Celecoxib, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study does not impact the benefit risk for Celecoxib and that there is no consequential regulatory action.

IV. SCIENTIFIC DISCUSSION

IV.1

Celecoxib is an oral non-steroidal anti-inflammatory and anti-rheumatic drug (NSAID) that has analgesic, anti-inflammatory and anti-pyretic activity. ATC code: M01AH01. It is a selective, cyclooxygenase-2 (COX-2) inhibitor which is believed to inhibit prostaglandin synthesis within the clinical dose range of 200-400mg daily. No statistically significant inhibition of COX-1 at this dose range was observed at this dose range in healthy volunteers. Celecoxib was observed to show reduced incidence of colonic tumour activity in animal models.

Celecoxib is available at several different strengths as hard capsules for oral use as follows:, 100mg and 200mg

There is no paediatric formulation.

Celecoxib received first regulatory approval on 31 December 1998 in the United States (US) and is currently approved in 135 countries and marketed in 125 countries. Celecoxib was developed and approved for the following indications: relief of the signs and symptoms of OA or RA; treatment of primary dysmenorrhea; and management of the signs and symptoms of ankylosing spondylitis (AS). In some markets, celecoxib is

also indicated for the management of acute pain in adults and relief of the signs and symptoms of juvenile idiopathic arthritis (JIA) in patients 2 years and older.

Celecoxib is not indicated for use in children in countries of the European Union.

IV.2 Clinical aspects

Juvenile idiopathic arthritis (JIA)

According to Orphan et al. Juvenile idiopathic arthritis (JIA) is the term used to describe a group of inflammatory articular disorders of unknown cause that begin before the age of 16 and last over 6 weeks. The term juvenile idiopathic arthritis was chosen to signify the absence of any known mechanism underlying the disorder and to highlight the necessity of excluding other types of arthritis occurring in well defined diseases (in particular arthritis occurring in association with infectious, inflammatory and haematologic/oncologic disease). The criteria that define the diseases are mainly clinical, but genetic studies (in particular linkage with HLA antigens) confirm that these are different disorders and not different clinical forms of a single disease.

Treatment of JIA is best managed in specialized centers where rheumatologists and paediatricians work in collaboration with physiotherapists, paediatric orthopaedic surgeons and psychologists to ensure global management of the medical aspects of the disease and its consequences on school and family life.

Celecoxib is indicated in the US for the relief of signs and symptoms of JRA (i.e., JIA categories that correspond to the former JRA classification system) in children aged 2-17 years. This indication was approved on 15 December 2006, based on data from Celecoxib Efficacy and Safety in JRA Patients, protocol N49-01-02-195 (clinical study 195), a randomised double-blind study comparing celecoxib to naproxen in 242 patients over a 12-week period with a 12-week open-label extension in which 202 patients participated, for a total of 100 patient-years of observation.

Celecoxib has received marketing authorization in 134 countries for OA, RA, JIA, AS, acute pain, primary dysmenorrhea, and as an adjunct to usual care in patients with familial adenomatous polyposis (FAP) in adults and/or children.

The familial adenomatous polyposis (FAP) indication was withdrawn in the USA on 04 Feb 2011 and was subsequently withdrawn worldwide by the MAH.

Celecoxib is not indicated for use in children in countries of the European Union.

The MAH submitted a final report for Study/Protocol No.: A3191342

A completed paediatric study for Celecoxib, Study/Protocol No.: A3191342, was submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on Celecoxib for paediatric use. The study title is: A Phase 4, 6-week, randomised, double-blind, multicentre, active, controlled trial, to evaluate the effects of celecoxib

(Celebrex) or naproxen on blood pressure in paediatric subjects with juvenile idiopathic arthritis.

2. Clinical study

Description

STUDY A3191342

A PHASE 4, 6-WEEK RANDOMIZED DOUBLE-BLIND- MULTICENTRE ACTIVE-CONTROLLED TRIAL TO EVALUATE THE EFFECTS OF CELECOXIB (CELEBREX) OR NAPROXEN ON BLOOD PRESSURE IN PEDIATRIC SUBJECTS WITH JUVENILE IDIOPATHIC ARTHRITIS

Description

This was a multicenter study in subjects with JIA, (oligoarticular, polyarticular arthritis and children with systemic onset disease but inactive systemic features), that included a screening phase (up to 2 weeks) followed by a 6-week, randomized, double-blind treatment phase.

All subjects from 2 to less than 18 years were randomized in a 1:1 ratio to either celecoxib (capsules, 50 mg twice daily [BID] or 100 mg BID) or naproxen (suspension, 7.5 mg/kg BID, maximum dose of 500 mg BID). Approximately 25 subjects were to be studied in the pre-pubertal ≥ 2 years to < 18 years age group in each of the treatment groups (celecoxib or naproxen).

The volume/dose of the study medications was determined by the subject's weight at Baseline visit. Blood pressure measurements were obtained from subjects using the cuff technique.

At Screening an optional blood sample was collected to explore possible association between cytochrome P450 (CYP) 2C9 genotypes and celecoxib's safety profile.

Participation in the 24-hour ambulatory blood pressure monitoring (ABPM) sub-study was open to all of the qualified sites that were participating in the main study. The minimum number of subjects to be enrolled in the ABPM sub-study was 20 subjects. Subjects participating in the sub-study needed to sign a separate ICF. Blood pressure was monitored by a 24-hour ambulatory BP device. The ABPM measurements were obtained in addition to the BP measurements obtained by the cuff technique. Standardized equipment (Space Labs 90207 monitor) for ABPM data collection was provided by a central vendor. If subjects decided to discontinue their participation in the ABPM sub-study, they could still continue their participation in the main study.

Methods

Each subject enrolled into the study was assigned a subject identification number (Subject ID). In order to randomize an appropriate subject, study personnel accessed the interactive voice response service (IVRS) system (via internet or telephone) to enroll

and obtain the randomization information for the subject. Study personnel then dispensed the randomized treatment allocation of drug, which corresponded to the allocation number as assigned by the IVRS system. According to a randomization schedule prepared by Pfizer, approximately 200 subjects were randomized in a 1:1 ratio to one of the following treatment groups:

- Celecoxib 50 mg or 100 mg BID (determined by subject's weight) or;
- Naproxen 7.5 mg/kg BID (maximum dose of 500 mg BID).

Objective(s)

The primary objective of the study was to evaluate the effect of treatment with Celecoxib on systolic blood pressure (SBP) compared to treatment with Naproxen in subjects with JIA (oligoarticular, polyarticular arthritis and children with systemic onset disease but inactive systemic features).

Secondary objectives of this study were to evaluate the:

1. Effect of treatment with celecoxib on diastolic blood pressure (DBP) compared to treatment with naproxen in subjects with JIA;
2. Adverse event profile and GI tolerability of treatment with Celecoxib vs. treatment with Naproxen in subjects with JIA;
3. Effect of treatment with celecoxib on Parent's and Subject's Global Assessment of Overall Well-Being compared to treatment with naproxen in subjects with JIA;
4. Effect of celecoxib and naproxen on BP measured by Ambulatory Blood Pressure Monitoring (ABPM) in subjects with JIA.

Overall Study Design and Plan:

This was a multicenter study in subjects with JIA, (oligoarticular, polyarticular arthritis and children with systemic onset disease but inactive systemic features), that included a screening phase (up to 2 weeks) followed by a 6-week, randomized, double-blind treatment phase.

All subjects from 2 to less than 18 years were randomized in a 1:1 ratio to either celecoxib (capsules, 50 mg twice daily [BID] or 100 mg BID) or Naproxen (suspension, 7.5 mg/kg BID, maximum dose of 500 mg BID). Approximately 25 subjects were to be studied in the pre-pubertal ≥ 2 years to < 18 years age group in each of the treatment groups (celecoxib or naproxen).

The volume/dose of the study medications was determined by the subject's weight at Baseline visit. Blood pressure measurements were obtained from subjects using the cuff technique.

At Screening an optional blood sample was collected to explore possible association between cytochrome P450 (CYP) 2C9 genotypes and celecoxib's safety profile.

An overview of the study design is provided in Figure 1

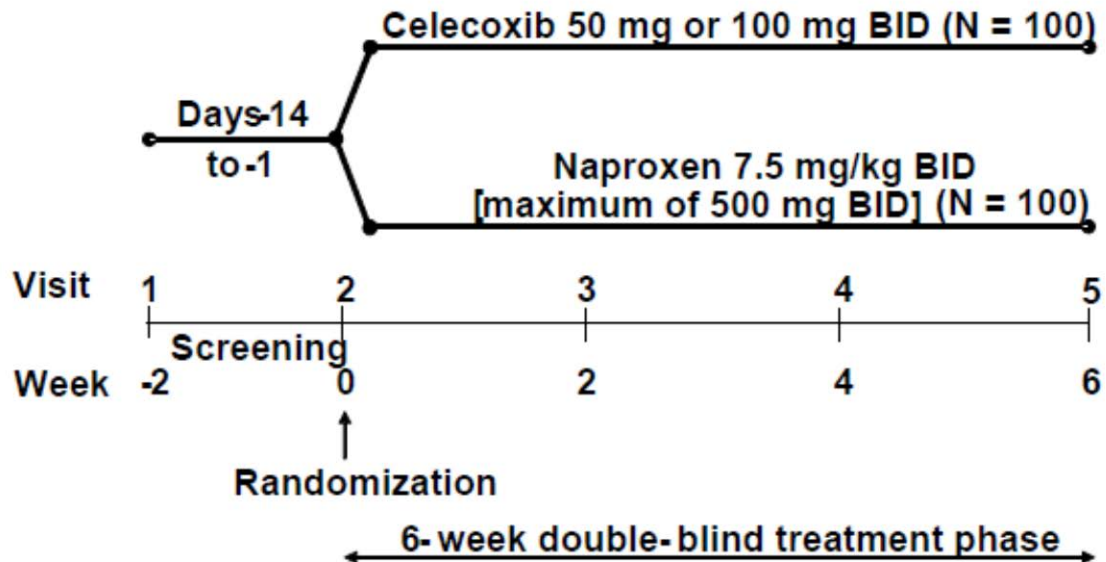


Figure 1: Study Design

Study population /Sample size

A sufficient number of subjects were enrolled to ensure that the objectives of the study be met. It was anticipated that approximately 100 subjects per treatment arm were required to meet the objectives of the study, of these 100 subjects, approximately 25 subjects were to be studied in the pre-pubertal ≥ 2 years to < 18 years age group in each treatment group.

Treatments

Double-blind investigational supplies of celecoxib and Naproxen were supplied by Pfizer. as described in Table 2 below

Table 2: Investigational Product

Treatment	Dosage	Study medication
Celecoxib	Subjects weighing ≥ 10 kg and ≤ 25 kg received 50 mg BID and Subjects weighing > 25 kg received 100 mg BID	50 mg capsules
		100 mg capsules
Naproxen	Approximately 7.5 mg/kg BID (maximum dose of 500 mg BID)	125 mg/5 mL suspension

If more than one batch of test drug/investigational product was used, refer to appendix 16.1.6 for details of subjects receiving each batch.

The median duration of treatment was 43.0 days for subjects in both treatment groups, which was consistent with the planned duration of the treatment (6 weeks). The majority of subjects were treated for 43 to 50 days; 57/100 subjects in the celecoxib group and 64/98 subjects in the Naproxen group.

Outcomes/endpoints

The efficacy endpoints were:

Change from baseline to Week 6/final visit in the Parent's/Guardian's Assessment of Overall Well-Being (marked as distance along a 100-mm long visual analogue scale [VAS]).

The number of subjects at Week 6/final visit with $\geq 30\%$ improvement in the Parent's/Guardian's Global Assessment of Overall Well-Being.

Change from baseline to Week 6/final visit in the Subject's Assessment of Overall Well-Being.

The number of subjects at Week 6/final visit with $\geq 30\%$ improvement in the Subject's Global Assessment of Overall Well-Being (marked as distance along a 100-mm long VAS).

The Safety endpoints were

Change From Baseline To Week 6/Final Visit In SBP

The primary safety endpoint of this study was the change from Baseline to Week 6/Final visit in SBP.

Change from Baseline to Weeks 2 and 4 In SBP and to Weeks 2, 4 and 6/Final visit In DBP .

24-Hour ABPM

After 6 weeks of treatment, both celecoxib and naproxen treated subjects exhibited small changes in 24-hour mean SBP relative to Baseline.

Statistical Methods

The Intent-to-Treat Population (ITT) included all subjects who were randomized to receive the study medication. The Safety Population included all randomized subjects who received at least one dose of study medication and this population was used to analyze all BP measurements (SBP, DBP). The Modified-Intent-to-Treat (MITT) Population included all randomized subjects who received at least one dose of study medication and had at least one post-baseline efficacy measurement. All efficacy variables were analyzed using the MITT population.

The primary and the secondary safety endpoints were analyzed using an analysis of covariance (ANCOVA) with model terms for treatment with baseline height, baseline weight, baseline age, and baseline BP as covariates. The LS mean change from Baseline and 90% (primary endpoint) or 95% confidence intervals (CIs) for the difference between the two treatment groups were generated.

Change from Baseline in BP was also analyzed using a repeated measures model for sensitivity analysis

The sample size calculation was based on the primary safety measure (change from Baseline to Week 6/Early termination in SBP). It was determined that a sample size of 100 subjects per treatment group would provide a 90% CI with an expected width of 4.42 mmHg. The standard deviation used for the sample size calculation was based on a previous study conducted by Pfizer in JIA subjects (Study N49-01-02-195) which yielded a standard deviation of 9.5 mmHg for the change in SBP.

Results

Recruitment/ Number analysed Planned:

200 subjects in total; 100 subjects each in the celecoxib and naproxen treatment groups.

Randomized: 201 (101 to Celecoxib and 100 to Naproxen)

Treated: 100 with Celecoxib, 98 with Naproxen

Completed: 88 Celecoxib, 94 Naproxen

Efficacy results

Change From Baseline To Week 6 / Final Visit In SBP

The primary safety endpoint of this study was the change from Baseline to Week 6/Final visit in SBP. The LS mean difference of SBP at Week 6/Final Visit relative to Baseline between celecoxib vs. naproxen treatment was 1.10 (90% CI: -0.56, 2.76) (Table S1). The 90% CI of the LS mean difference of SBP between the treatments included zero (0), indicating with 90% confidence that no treatment difference was a possibility. The LS mean changes from Baseline to Week 6/Final Visit in SBP were 0.37 mmHg in the celecoxib group and -0.73 mmHg in the Naproxen group.

Table S1: Change from Baseline to Week 6/Final Visit in Systolic Blood Pressure – Safety Population

Value	Celecoxib N=100	Naproxen N=98
Baseline		
n	98	98
Mean (SD)	98.5 (9.49)	98.1 (9.49)
Median (Min, Max)	99.3 (80, 123)	99.5 (76, 128)
Week 6/Final Visit		
n	98	98
Mean (SD)	98.9 (8.84)	97.4 (10.33)
Median (Min, Max)	99.0 (80, 122)	97.0 (80, 131)
Mean Change from Baseline (SD)	0.3 (7.06)	-0.7 (8.10)
Median Change from Baseline (Min, Max)	0.0 (-19, 20)	-0.2 (-21, 25)
LS Mean Change (SE)	0.366 (0.70)	-0.734 (0.70)
Difference Celecoxib – Naproxen		
LS Mean (SE)	1.100 (1.004)	
90% CI	-0.56, 2.76	

Abbreviations: CI=confidence interval; DBP=diastolic blood pressure; LS=least square; Max=maximum; Min=minimum; N, n=number; SBP=systolic blood pressure; SD=standard deviation; SE=standard error.

The change from baseline in blood pressure was analyzed using an ANCOVA model with terms for treatment, baseline height, weight, age and baseline blood pressure as covariates. For early terminations the last observation carried forward (LOCF) was used to impute missing data. For each clinic visit, the average of the 3 SBP measurements and the average of the 3 DBP measurements was calculated and used as each subject's respective BP response. Blood pressure readings were taken in the sitting position.

Change from Baseline to Weeks 2 and 4 In SBP and to Weeks 2, 4 and 6/Final visit In DBP

The LS mean differences of SBP at Weeks 2 and 4 relative to Baseline between celecoxib vs. naproxen treatment were 1.09 (95% CI: -0.39, 2.57; p=0.148) and 1.84 (95% CI: 0.21, 3.46; p=0.027), respectively. The 95% CIs of the LS mean differences of SBP between the treatments at Week 2 included zero (0), indicating with 95%

confidence that no treatment difference at Week 2 was a possibility. The 95% CIs of the LS mean differences of SBP between the treatments at Week 4 excluded zero (0), indicating the possibility that the SBP decreases relative to Baseline were higher for naproxen than for celecoxib treatment. The LS mean changes in SBP from Baseline to Weeks 2 and 4 were -0.20 mmHg and -0.17 mmHg in the celecoxib group and -1.29 mmHg and -2.00 mmHg in the Naproxen group.

The LS mean differences of DBP at Weeks 2, 4, and 6/Final Visit relative to Baseline between celecoxib vs. naproxen treatment were -1.21 (95% CI: -2.67, 0.26; $p=0.106$) at Week 2, -0.22 (95% CI: -1.30, 1.74; $p=0.776$) at Week 4, and -0.18 (95% CI: -1.69, 1.33; $p=0.815$) at Week 6/Final Visit.

The 95% CIs of the LS mean differences in DBP between the treatments included zero (0) at Weeks 2, 4 and 6/Final Visit, indicating with 95% confidence that no treatment differences at Weeks 2, 4 and 6/Final Visit were a possibility. The LS mean changes in DBP from Baseline to Weeks 2, 4 and 6/Final Visit were -1.35 mmHg, -0.63 mmHg and -0.54 mmHg in the celecoxib group, and -0.14 mmHg, -0.85 mmHg and -0.36 mmHg in the Naproxen group, respectively.

24-Hour ABPM

After 6 weeks of treatment, both celecoxib and naproxen treated subjects exhibited small changes in 24-hour mean SBP relative to Baseline: subjects in the celecoxib group experienced an increase of the mean (SD) SBP of 2.4 ± 7.0 mmHg while subjects in the naproxen group experienced a decrease of -1.7 ± 12.4 mmHg. A single subject randomized to naproxen exhibited clinically implausible blood pressure decreases over the course of the 24-hour ABPM and an outlier analysis was performed. This resulted in an increase of the ABPM mean SBP relative to Baseline by 1.9 ± 4.1 mmHg for the naproxen group. These increases, of about 2 mmHg for SBP and less than 1 mmHg for DBP, were similar for both drugs and considered as not clinically relevant

Adverse events

The proportion of subjects reporting all-causality TEAEs was similar between the treatment groups (Table S2). Overall, 48 (48.0%) subjects in the celecoxib group and 47 (48.0%) subjects in the Naproxen group reported 82 and 83 all-causality TEAEs, respectively. The number and proportion of subjects reporting treatment-related TEAEs was slightly lower in the celecoxib group compared with the naproxen group; 13 (13.0%) vs. 20 (20.4%) subjects.

The majority of all TEAEs were graded CTC 1 and 2. In the celecoxib group, 2 subjects reported TEAEs of CTC Grade 3 or 4; both events were not considered by the investigator to be related to study drug treatment. No deaths related to AEs occurred in the study.

One SAE (hand fracture) was reported in the naproxen group, which was not considered to be related to study drug treatment.

Commonly reported all-causality TEAEs (incidence of $\geq 5\%$ in any treatment group) included nausea, headache, and arthralgia. For nausea in both treatment groups and

headache in the Naproxen group, the majority of events were considered treatment-related.

Rapporteur's comment

Regarding Study A3191342 the objectives have been achieved as follows:

Primary objective:

Regarding the primary objective to compare the effect of treatment with celecoxib on systolic blood pressure (SBP) to treatment with naproxen in subjects 2 to 18 years with juvenile idiopathic arthritis (JIA) , oligoarticular, polyarticular arthritis with systemic onset disease but inactive features the study showed that:

The primary end point analysis of SBP from Baseline to week 6/Final visit did not indicate differences between treatments with celecoxib and naproxen.

Secondary objectives:

Regarding the evaluation of the effect of treatment with celecoxib on diastolic blood pressure (DBP) compared to treatment with naproxen in children 2 to 18 years with JIA showed that:

There was no indication of a difference between celecoxib and naproxen treatments for the SBP changes from Baseline to week 2 and for the difference of DBP changes from Baseline to Weeks 2, 4 and 6/Final visit.

Regarding the adverse events profile and gastro-intestinal tolerability of treatment with celecoxib vs. treatment with naproxen in the study population of children with JIA it was shown:

There were no deaths. 5% of subjects on celecoxib withdrawal from treatment because of adverse events including worsening of JIA. The safety and tolerability of celecoxib were consistent with the known safety profile for this drug. No new safety concerns were identified in the children of this study.

Regarding the evaluation of the effect of treatment with celecoxib on Parents' and Subjects' Global Assessment of Overall Well being compared to treatment with Naproxen In children with JIA in this study:

No statistically significant differences were revealed between the two treatments at week 6/Final visit relative to Baseline.

Regarding the evaluation of the effect of celecoxib and naproxen on blood pressure (BP) measured by Ambulatory Blood Pressure Monitoring (ABPM) in the study population it was found that:

Small and similar increases of SBP of no known clinical relevance were observed at the Week 6/Final visit relative to Baseline upon treatment with celecoxib and naproxen (excluding an outlier with implausible results).

The findings of the study are endorsed.

In conclusion the study did not reveal any findings which would warrant a change to be made in the SmPC.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

Overall conclusion

Basing on the data submitted by the MAH the Rapporteur agrees that the benefit risk for celecoxib is unchanged and that there is no need for any consequential regulatory action leading to amendments to the product information in the SmPC or PL

Following submission of the Day 70 PdAR by the Rapporteur, the Member States were in agreement with the recommended conclusions.

The Rapporteur therefore in this Public Paediatric Assessment Report recommends no changes to the celecoxib Summary of Product Characteristics (SmPC) and Package Leaflet (PL).

Recommendation

In connection with this Paediatric Work Sharing (PdWS) procedure according to Article 46 of the Paediatric Regulation (EC) no 1901/2006 as amended, basing on a review of the paediatric data submitted by the MAH regarding the treatment of children with celecoxib, procedure number MT/W /010 /PdWS /001, and based on current literature regarding the safety of celecoxib, no SmPc and no PL changes are required.

No further action required.