Medicines Adverse Reactions Committee

Meeting date	**8 March 2018**	Agenda item	3.2.4
Title	**NSAIDs and cardiovascular risk**		
Submitted by	Medsafe Clinical Risk Management Team	Paper type	For advice
Active constituent Celecoxib	**Medicines** Celecoxib Pfizer	**Sponsors** Pfizer	
International action	Since 2005 there has been a FDA boxed warning for NSAIDs regarding cardiovascular (CV) risk. In 2015, the FDA strengthened the existing label warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) increase the chance of a MI or stroke. At that time, the FDA required updates to the drug labels of all prescription NSAIDs, and OTC non-aspirin NSAID Drug Facts labels (see Annex 1: FDA Drug Safety Communication). https://www.fda.gov/Drugs/DrugSafety/ucm451800.htm		
Previous MARC meetings	NSAIDs and CV risk has been discussed previously, most recently at the following meeting: – 154th Meeting — 13 June 2013 Diclofenac and cardiovascular risk Prior to the 2013 discussion, the Committee last formally reviewed the safety of NSAIDs in December 2007		
Prescriber Update	September 2013 article notes that: "All non-steroidal anti-inflammatory drugs (NSAIDs) are associated with a small increased risk of serious cardiovascular adverse events." It was further noted that: "The risk is increased with high doses, increasing duration of use and in patients with other cardiovascular risk factors." May 2008 Prescriber Update article explains that datasheets for all non-selective NSAIDs were to include warnings about cardiovascular risks, as well as about skin and gastrointestinal risks.		
Schedule	Prescription medicine		
Usage data	There were 112,588 community dispensed prescriptions for celecoxib in 2017.		
Advice sought	**The Committee is asked to advise whether:** – the proposed draft celecoxib datasheet contraindications and warnings are appropriate – there should be similar contraindications and warning regarding cardiovascular disease risk for all non-aspirin NSAIDs, including COX-2 inhibitors.		

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1.0 PURPOSE

Medsafe is seeking MARC advice about appropriate datasheet contraindications and warnings regarding CV risk of celecoxib, and regarding non-steroidsal anti-inflammatory drugs (NSAIDs) generally.

Medsafe has received a Changed Medicine Notification (CMN) from Pfizer regarding the datasheet of Celecoxib Pfizer (celecoxib), 100 mg and 200 mg capsules. The CMNs seeks to relocate the contraindication for patients with significant established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease to the precaution section.

The CMN is supported by the results from the Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen Or Naproxen (Precision) Study [Study A3191172]. There are three annexes related to the Precision study.

- Annex 2: the Medsafe evaluation report of the information received about the study as part of this CMN application; Celecoxib: relocating contraindication regarding established CV disease to precautions, February 2018.
- Annex 3: Nissen 2016, the NEJM article about the Precision study.
- Annex 4: the Pepine 2017 article that comments on the Precision study.

2.0 BACKGROUND

2.1 Celecoxib

2.1.1 Cox-1 and Cox-2

Celecoxib was developed to reduce the adverse GI effects associated with the non-selective NSAIDs while maintaining beneficial properties for arthritic pain. Inhibition of cyclooxygenase (COX) is the common mechanism of action of NSAIDs. The COX enzyme exists in 2 forms:

- constitutive form - COX-1 is normally produced in a wide variety of tissues and organs, including the stomach, platelets, and kidneys. Prostaglandins (PGs) produced as a result of COX-1 activity participate in “housekeeping” cell functions.
- inducible form - in contrast, COX-2 is mainly produced in association with inflammation, neoplasia, and growth, where PGs act as pro-inflammatory mediators.

NSAIDs vary in the extent to which they inhibit Cox-1 and Cox-2 enzymes.

- Naproxen is mostly a Cox 1 inhibitor (expect adverse GI effects), slight Cox 2 effect.
- Ibuprofen inhibits both COX-1 and COX- 2.
- Celecoxib is mostly a Cox 2 inhibitor. Celecoxib is an NSAID that exhibits analgesic, anti-inflammatory, and antipyretic activities in animal models.

2.1.2 Descriptions of proposed datasheet changes

<u>Contraindications</u>

Current datasheet

> Celecoxib Pfizer is contraindicated in:
>
> Patients with unstable or significant established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease (see section 4.4).
>
> Patients with congestive heart failure (NYHA II-IV).

Proposed

The contraindication regarding "significant established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease" is proposed to be relocated to the Precautions section, so the contraindication will read as follows:

> Celecoxib Pfizer is contraindicated in:
>
> Patients with unstable ischaemic heart disease of thrombus aetiology.
>
> Patients with congestive heart failure (NYHA II-IV).

Special Warnings and Precautions for use/ Cardiovascular Effects

Below, solely the changed paragraph is provided. In the 'datasheets' section below in this report the full 'warnings' regarding CV risk is reproduced.

Current datasheet

> Two large, controlled clinical trials of a different COX-2 selective inhibitor for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. In the absence of comparable data with celecoxib, it may be assumed that patients at high risk of CV disease (including patients with diabetes, ischaemic heart disease, cardiac failure, hyperlipidaemia, hypertension, or smokers) who are undergoing any major surgery may face an increased risk of developing a CV event. **Patients with significant risk factors for CV events should only be treated with celecoxib after careful consideration of the patient's overall risk and the potential risks and benefits of alternative analgesic therapies.**

Proposed

> Two large, controlled clinical trials of a different COX-2 selective inhibitor for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. In the absence of comparable data with celecoxib, it may be assumed that patients at high risk of CV disease (including patients with diabetes, ischaemic heart disease, cardiac failure, hyperlipidaemia, hypertension, or smokers) who are undergoing any major surgery may face an increased risk of developing a CV event. **Patients with significant established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease as well as patients with significant and multiple risk factors for CV events should only be treated with celecoxib after careful consideration of the patient's overall risk and the potential risks and benefits of alternative analgesic therapies.**

Special studies

In the following section, details regarding the Precision study, including the ABPM Substudy, are inserted.

> 5. PHARMACOLOGICAL PROPERTIES
>
> 5.1 Pharmacodynamic properties
>
> Special studies

Comments

The Pfizer Changed Medicine Notification application being considered by Medsafe proposes the reduction of the information regarding risk for patients with established CVD disease. That is; "significant established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease" is moved from the contraindication to the precaution section of the datasheet.

2.2 Risk of cardiovascular disease with NSAIDs

Identification of cardiovascular (CV) risk led to the withdrawal of the Cox-2 inhibitor rofecoxib [Vioxx]. Timelines include the following:

- 1998 - Celecoxib approved. Two other COX-2 inhibitors were subsequently approved by the FDA - rofecoxib [Vioxx] in 1999, and valdecoxib in 2001.
- 2004 - Vioxx (rofecoxib) was withdrawn from the market.
- 2005 - FDA boxed warning regarding CV risk for all NSAIDs.
- 2006 – start of Pfizer sponsored Precision study regarding NSAIDs and CV risk.
- 2015 - FDA strengthened the existing label warning that NSAIDs increase the chance of a MI or stroke.

Although the mechanism by which NSAIDs increase CV risk is not known, the risk appears increased throughout the time that NSAIDs are taken, even in the short term.

According to The FDA Drug Safety Communication, estimates of increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, range from 10 percent to 50 percent or more, depending on the drugs and the doses studied.

The FDA Communication further notes that patients with known cardiovascular disease or risk factors had a higher absolute incidence of serious cardiovascular thrombotic events conferred by NSAID use due to their increased baseline rate.

Comments

The risks associated with NSAIDs are serious as they include MI and stroke that can lead to death. However, these events are uncommon and NSAID use increases the risk only moderately (up to 50%).

The risk is, therefore, particularly relevant to patients with high baseline risk of CV events.

2.3 Uncertainty whether NSAID CV risk applies to all NSAIDs equally

2.3.1 US

As noted above, there has been a FDA safety communication about NSAIDs and CV risk since 2005, which was strengthened in 2015.

2.3.2 Health Canada

Following the Bhala 2013 publication regarding the Coxib and NSAID Trialists' (CNT) Collaboration meta-analysis (see Scientific Information section below), Health Canada provided information on their website.

A summary safety review regarding celecoxib's risk of CV disease relative to other NSAIDs in April 2016 notes the findings of the CNT Collaboration meta-analysis:

> … that celecoxib (at doses of higher than 200 mg per day) may be linked with an increased risk of serious heart and stroke related side effects and this risk is similar to the risks linked with the use of high doses of diclofenac (≥150 mg per day) or ibuprofen (≥2400 mg per day).

In addition: "Based on a review of the available data, a relative ranking of NSAIDs in terms of their cardiovascular safety could not be carried out at this time." (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/safety-reviews/summary-safety-review-celebrex-generics-assessing-risk-serious-heart-stroke-high-doses.html)

2.3.3 EMA

The EMA advised in May 2015 that, following a Pharmacovigilance Risk Assessment Committee (PRAC) review, the CV risk with high-dose ibuprofen is similar to the risk seen with some other non-steroidal anti-inflammatory drugs (NSAIDs), including COX-2 inhibitors and diclofenac (EMA/325007/2015,). (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Ibuprofen_and_dexibuprofen_containing_medicines/human_referral_prac_000045.jsp&mid=WC0b01ac05805c516f).

2.3.4 NHS

A recent summary provided by the NHS Medicines Update regarding oral NSAIDs (6 August 2017), highlights the need to avoid all NSAIDs in patients with a history of vascular disease, a high risk of cardiovascular disease, or gastrointestinal risk factors. The wording suggests a contraindication, for example, "Avoid NSAIDs if possible in patients with CVD". The statement appears to apply to all NSAIDs, including Cox-2 inhibitors (see Annex 5: NHS Medicines Update regarding oral NSAIDs).

In addition, later in the update Cox-2 selective inhibitors are mentioned separately. It is noted that: "Cox-2 selective inhibitors have been associated with an increased risk of CV events". (www.ggcprescribing.org.uk/media/uploads/ps_extra/mu_extra_06_nsaids_2017.pdf)

2.4 Datasheets

Selected datasheets are considered below, and guidance about what constitutes a contraindication is noted.

While in Europe there is a contraindication regarding established CV disease for Cox-2 inhibitors, in the US the contraindication is specific to use related to the setting of CABG surgery.

In addition, in the US, label contraindications and warnings are harmonised across all non-aspirin NSAIDs including Cox-2 inhibitors.

2.4.1 New Zealand

In New Zealand, celecoxib is contraindicated for the relatively large group of patients with established cardiovascular disease. A lesser population has naproxen contraindicated: those undergoing CABG and those with severe heart failure. For ibuprofen, the contraindication applies to a further subgroup; patients with severe heart failure.

- The **Celecoxib** current datasheet has that Celecoxib Pfizer is contraindicated in:

  • Patients with unstable or significant established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease (see section 4.4).

- The **naproxen** datasheet (Noflam) on the Medsafe website (as at 25 January 2018) includes the following contraindications among others:

  NOFLAM is contraindicated in patients:

  - with severe heart failure.
  - undergoing treatment of perioperative pain in setting of coronary artery surgery (CABG).

- The **ibuprofen** datasheet has that it is contraindicated in severe heart failure (NYHA IV). There are also warnings regarding cardiovascular thrombotic events.

Warnings and Precautions

- The **Celecoxib** current datasheet warning includes:

COX-2 inhibitors, including celecoxib, have been associated with an increased risk of serious CV thrombotic adverse events, myocardial infarction and stroke, which can be fatal (see section 5.1, Clinical Efficacy and Safety, Cardiovascular Safety).

All NSAIDs, both COX-2 selective and non-selective may cause an increased risk of serious CV thrombotic events. This risk may increase with dose and duration of use. The relative increase of this risk appears to be similar in those with or without known CV disease or CV risk factors. However, patients with CV disease or CV risk factors may be at greater risk in terms of absolute incidence, due to their increased rate at baseline.

Two large, controlled clinical trials of a different COX-2 selective inhibitor for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. In the absence of comparable data with celecoxib, it may be assumed that patients at high risk of CV disease (including patients with diabetes, ischaemic heart disease, cardiac failure, hyperlipidaemia, hypertension, or smokers) who are undergoing any major surgery may face an increased risk of developing a CV event. Patients with significant risk factors for CV events should only be treated with celecoxib after careful consideration of the patient's overall risk and the potential risks and benefits of alternative analgesic therapies.

To minimise the potential risk for an adverse CV event in patients treated with celecoxib, the lowest effective dose should be used for the shortest duration possible (see section 4.2).

Prescribers should inform the individual patient of the possible increased risks when prescribing celecoxib for patients at high risk of CV adverse events. Physicians and patients should remain alert for such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and symptoms of serious CV toxicity and the steps to take if they occur. Celecoxib is not a substitute for CV prophylaxis because of its lack of effect on platelets; therefore, concurrent anti-platelet therapies should not be discontinued. There is no evidence that concurrent use of aspirin decreases the risk of CV adverse events associated with COX-2 inhibitors, including celecoxib.

- The **naproxen** datasheet (Noflam) warnings include:

  Observational studies have indicated that non-selective NSAIDs may be associated with an increased risk of serious cardiovascular events, including myocardial infarction and stroke, which may increase with dose or duration of use. Patients with cardiovascular disease, history of atherosclerotic cardiovascular disease or cardiovascular risk factors may also be at greater risk.

  To minimise the potential risk of an adverse cardiovascular event in patients taking an NSAID, especially in those with cardiovascular risk factors, the lowest effective dose should be used for the shortest possible duration.

  Physicians and patients should remain alert for such CV events even in the absence of previous CV symptoms. Patients should be informed about signs and/or symptoms of serious CV toxicity and the steps to take if they occur.

  There is no consistent evidence that the concurrent use of aspirin mitigates the possible increased risk of serious cardiovascular thrombotic events associated with NSAID use.

Clinical trial and epidemiological data suggest that the use of coxibs and some NSAIDs (particularly at high doses or long-term treatment) may be associated with a small increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke).

Comments

The current and proposed Celecoxib datasheet warnings section adequately covers the following:

- *The increased risk of serious CV thrombotic adverse events, myocardial infarction and stroke, which can be fatal.*
- *All NSAIDs, both COX-2 selective and non-selective may cause an increased risk of serious CV thrombotic events.*
- *This risk may increase with dose and duration of use.*
- *The relative increase of this risk appears to be similar in those with or without known CV disease or CV risk factors. However, patients with CV disease or CV risk factors may be at greater risk in terms of absolute incidence, due to their increased rate at baseline.*

- The **ibuprofen** datasheet warnings include the following.

  Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400 mg/day), may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (≤ 1200 mg/day) is associated with an increased risk of arterial thrombotic events.

  Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses (2400 mg/day) should be avoided.

  Careful consideration should also be exercised before initiating long term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking), particularly if high doses of ibuprofen (2400 mg/day) are required.

  There is no consistent evidence that the concurrent use of aspirin mitigates the possible increased risk of serious cardiovascular thrombotic events associated with NSAID use.

Comment

The current Ibuprofen datasheet (which mirrors the UK approved PI) does not cover the following warnings (warnings which are, for example, contained in the US product information for NSAIDs):

- *Ibuprofen at high doses may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal.*
- *All NSAIDs may have a similar risk.*
- *This risk may increase with duration of use.*
- *Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.*

2.4.2 UK and US general guidance on what constitutes a contraindication

The general guidance on what constitutes a contraindication in product information is similar in the UK and US.

- The guideline on summary of product characteristics (SmPC), September 2009 notes that a contraindication is appropriate for situations where the medicinal product must not be given for safety reasons.
- In the US, guidance on labelling (October 2011) "Guidance for industry; warnings and precautions, contraindications, and boxed warnings section of labelling for human prescription drug and biological products – content and format" gives a high threshold for a risk to constitute a contraindication; use should clearly outweigh any possible or potential therapeutic benefit to any patient.

  The US has, however, boxed warnings to highlight an AE so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the drug.

Comment
In New Zealand the SmPC guideline was adopted for the format of data sheets.

2.4.3 UK

The EMC webpage regarding **Celecoxib** capsules includes the following among contraindications.

> Congestive heart failure (NYHA II-IV).
>
> Established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

The warnings include:

> Cardiovascular effects
>
> Increased number of serious cardiovascular events, mainly myocardial infarction, has been found in a long-term placebo-controlled study in subjects with sporadic adenomatous polyps treated with celecoxib at doses of 200 mg BID and 400 mg BID compared to placebo (see section 5.1).
>
> As the cardiovascular risks of celecoxib 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 (see sections 4.2, 4.3, 4.8 and 5.1).
>
> Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with celecoxib after careful consideration (see section 5.1).
>
> COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thrombo-embolic diseases because of their lack of antiplatelet effects. Therefore, antiplatelet therapies should not be discontinued (see section 5.1).

The information with **naproxen** suggests that there may be no marked difference in CV risk between Cox-2 inhibitors and NSAIDs generally. The naproxen tablets SmPC (last updated on eMC on 7 Sep 2016) includes among contraindications:

> Severe heart failure, hepatic failure and renal failure

The warnings include:

> *Cardiovascular and cerebrovascular effects*

> Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.
>
> Clinical trial and epidemiological data suggest that use of coxibs and some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Although data suggest that the use of naproxen (1000mg daily) may be associated with a lower risk, some risk cannot be excluded.
>
> Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with naproxen after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

The **Brufen (ibuprofen)** SmPC (last updated on eMC on 12 Sep 2016) includes among contraindications:

> Brufen is contraindicated in patients with severe heart failure (NYHA Class IV), hepatic failure and renal failure

The warnings include:

> *Cardiovascular and cerebrovascular effects*
>
> Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.
>
> Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400 mg/ day) may be associated with a small increased risk of arterial thrombotic events such as myocardial infarction or stroke. Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. ≤ 1200mg/day) is associated with an increased risk of arterial thrombotic events.
>
> Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses (2400mg/day) should be avoided. Careful consideration should also be exercised before initiating long-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking), particularly if high doses of ibuprofen (2400mg/day) are required.

2.4.4 US

Although the uncertainty regarding CV risk applying equally to all NSAIDs is acknowledged, the US FDA contraindications and warning for all NSAIDs are similar.

The black box warning for Celebrex regarding Cardiovascular Risk includes among other information:

- In addition to hypersensitivity, the contraindications [also copied in the black box warning] include “Use during the perioperative period in the setting of coronary artery bypass graft (CABG) surgery”.
- CELEBREX, may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs may have a similar risk. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (5.1,14.7)

A similar contraindication is found in the label for NAPRELAN (naproxen sodium) Controlled-Release Tablets for oral use, the black box warning includes:

> Naproxen as NAPRELAN® is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (See WARNINGS).

The above black box text is repeated in the contraindications section later in the PI:

> In the setting of coronary artery bypass graft (CABG) surgery [see Warnings and Precautions (5.1)]

Warnings and Precautions

- The **Celecoxib** label warning includes:

  > Chronic use of CELEBREX may cause an increased risk of serious adverse cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. In the APC (Adenoma Prevention with Celecoxib) trial, the hazard ratio for the composite endpoint of cardiovascular death, MI, or stroke was 3.4 (95% CI 1.4 – 8.5) for CELEBREX 400 mg twice daily and 2.8 (95% CI 1.1 – 7.2) with CELEBREX 200 mg twice daily compared to placebo. Cumulative rates for this composite endpoint over 3 years were 3.0% (20/671 subjects) and 2.5% (17/685 subjects), respectively, compared to 0.9% (6/679 subjects) with placebo treatment. The increases in both celecoxib dose groups versus placebo-treated patients were mainly due to an increased incidence of myocardial infarction
  >
  > All NSAIDs, both COX-2 selective and non-selective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with CELEBREX, the lowest effective dose should be used for the shortest duration consistent with individual patient treatment goals. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV toxicity and the steps to take if they occur.

- For **naproxen** the label includes the following.

  > Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.
  >
  > There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as naproxen, increases the risk of serious gastrointestinal (GI) events [see Warnings and Precautions (5.2)].
  >
  > Status Post Coronary Artery Bypass Graft (CABG) Surgery
  >
  > Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10–14 days following CABG surgery found an increased incidence of

myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG [see Contraindications (4)].

Post-MI Patients

Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post-MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

Avoid the use of NAPRELAN in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If NAPRELAN is used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

2.4.5 Summary tables

Table 1 summarises settings or populations with conditions to which contraindications apply.

Table 1: Settings or populations with conditions to which contraindications apply

	US	***UK***	***NZ***
	Celecoxib		
Setting of CABG	*Yes*		
Severe heart failure		*Yes**	
Established CV disease		*Yes*	*Yes*
Cerebrovascular disease		*Yes*	*Yes*
Peripheral artery disease		*Yes*	*Yes*
	Naproxen		
Setting of CABG	*Yes*		*Yes*
Severe heart failure		*Yes*	*Yes*
Established CV disease			
Cerebrovascular disease			
Peripheral artery disease			
	Ibuprofen		
Setting of CABG	*Yes*		
Severe heart failure		*Yes*	*Yes*
Established CV disease			
Cerebrovascular disease			
Peripheral artery disease			

* congestive (rather than severe) heart failure

Comment

To be a contraindication, conditions should have particularly high risk of CV events; for example, patients undergoing CAGB (US), severe heart failure (NZ, for naproxen), heart failure (UK), and unstable angina (NZ, 'unstable ischemic heart disease' for celecoxib).

All of these conditions could occur in a setting of need for moderate analgesia, even if only because of co-existing conditions.

The **warnings** usually include that the particular NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. US PI and New Zealand datasheets for celecoxib and naproxen include a sentence such as the following.

> To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible.

Additional factors are variously noted (see table below)

Table 2: Factors regarding risk noted in 'warnings' section

	US	***UK***	***NZ***
	Celecoxib		
Dose effect	*Yes*	*Yes*	*Yes*
Duration effect	*'chronic use' plus 'lowest effective dose should be used for the shortest duration'*	*Yes*	*Yes*
Importance for those with risk factors	*Yes*	*Yes*	*Yes*
All NSAIDs may have a similar risk	*Yes*		*Yes*
Naproxen, or low dose ibuprofen, less risk		*Yes*	
	Naproxen		
Dose effect	*Yes*		*lowest effective dose should be used for the shortest possible duration*
Duration effect	*lowest effective dose should be used for the shortest duration*	*Yes*	*Yes*
Importance for those with risk factors	*yes*	*yes*	*Yes*
All NSAIDs may have a similar risk	*Yes*		
Naproxen, or low dose ibuprofen, less risk		*risk applies to coxibs and some NSAIDs*	
	Ibuprofen		
Dose effect	*NA*	*Yes*	*Yes*
Duration effect	*NA*		
Importance for those with risk factors	*NA*	*Yes*	*Yes*
All NSAIDs may have a similar risk	*NA*		
Naproxen, or low dose ibuprofen, less risk	*NA*	*Yes*	*Yes*

3.0 SCIENTIFIC INFORMATION

3.1 Published literature

3.1.1 Bhala, 2013

The Coxib and NSAID Trialists' (CNT) Collaboration meta-analysis used individual participant clinical trial data (where available) from a large number of clinical trials on both COX-2 selective agents (including celecoxib), and traditional NSAIDs.

As the study used data from randomised trials, the meta-analysis is unaffected by selection and other biases inherent in observational studies. However, in the analyses, treatment effects were estimated by comparing the results of trials of a coxib versus placebo and trials of a coxib versus tNSAID (traditional NSAIDs). The authors note that the conditions under which such indirect comparisons might be expected to yield valid results are satisfied, since the two sets of trials involved similar doses of coxibs and similar populations, and different studies used the same (high-dose) tNSAID regimens as comparators.

The primary vascular outcome was major vascular events, defined as non-fatal myocardial infarction, non-fatal stroke, or death from a vascular cause. Results from CNT concluded that "The vascular risks of high-dose diclofenac, and possibly ibuprofen, are comparable to coxibs, whereas high-dose naproxen is associated with less vascular risk than other NSAIDs."

For another endpoint, the risk of hospitalisation due to heart failure, there was roughly a doubling of risk with all NSAID regimens studied (including naproxen).

3.1.2 MacDonald, 2016

Data from the Standard Care vs. Celecoxib Outcome Trial (SCOT) was published one month prior to the November 2016 public disclosure of the Precision results (MacDonald et al, 2016).

Patients aged 60 years and over with osteoarthritis or rheumatoid arthritis, free from established CV disease and taking chronic prescribed nsNSAIDs, were randomized to switch to celecoxib or to continue their previous nsNSAID.

The primary outcome measure was the first occurrence of hospitalization or death for the APTC cardiovascular endpoint of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death. It was conducted in the UK, Denmark, and the Netherlands.

In total, 7,297 participants were randomized. Mean follow-up 3.2 years [fewer subjects than expected signed up to take part in the study - to compensate, follow-up was extended.] Subjects could not have established CV disease, but often had risk factors (including age, hypertension). Events were obtained through hospital/death records making detailed adjudication quite difficult.

The difference in the rate of on-treatment primary CV event was not statistically significantly different:

- celecoxib, 0.95 per 100 patient-years,
- nsNSAIDs, 0.86 per 100 patient-years (HR =1.12, 95% confidence interval, 0.81–1.55).

The authors concluded that, in subjects 60 years and over who are free from CV disease and taking prescribed chronic non-selective NSAIDs, CV events were infrequent and similar to celecoxib.

3.1.3 Nissen, 2016 (Annex 3)

The authors conclude that the Precision study shows that at moderate doses, celecoxib was noninferior to ibuprofen or naproxen with regard to cardiovascular safety (see Annex 3: Nissen 2016).

The evaluator's summary of the Precision study is provided in the 'company report' section below. In addition, a copy of the Pepine 2017 article that comments on the Precision study is also provided (see Annex 4: Pepine 2017).

3.1.4 Sondergaard 2017 (Annex 6)

A Danish self-controlled study assessed the risk of out-of-hospital cardiac arrest (OHCA) with exposure to NSAIDs (via redeemed prescriptions) identified 28 947 persons with OHCA during 2001–10. Ibuprofen was the most commonly prescribed NSAID followed by diclofenac comprising 51.0% and 21.8% of total NSAIDs, respectively (see Annex 6).

This case–time–control study compared,

- exposure to NSAIDs 30 days before cardiac arrest (case period)
- exposure to NSAIDs in a preceding 30-day period where the individual did not experience an event (control period).

A 30-day washout period separated case and control period to eliminate possible carry-over effects.

Use of any NSAID was associated with a significantly increased risk of cardiac arrest, OR 1.31 (95% confidence interval (CI) 1.17–1.46).

The result was primarily driven by an increased risk of cardiac arrest in ibuprofen and diclofenac users.

Lack of statistical power was accepted as explaining the lack of significant association between cardiac arrest and use of the COX-2 selective inhibitors, rofecoxib and celecoxib, nor with the unselective NSAID naproxen.

3.1.5 Bally, 2017 (Annex 7)

A recent meta-analysis' findings are consistent with that of the Precision study.

The Bally study used individual-patient data (IPD) from four administrative data sets that had been previously collected from large cohort studies. These data have previously been used for nested case control studies (that is; the information for cases and controls were drawn from the population in a fully enumerated cohort) (see Annex 7).

In the data, MI was documented separate from other cardiovascular outcomes. The pooled data comprised 61,460 cases and 385,303 controls. For example in the contributing Finnish study, controls were identified from a population register, with NSAID exposure data sourced from the Finnish Prescription Register and the Special Reimbursement Register. [Helin-Salmivaara A, Virtanen A, et al. NSAID use and the risk of hospitalization for first myocardial infarction in the general population: a nationwide case-control study from Finland. Eur Heart J 2006;27:1657-63. doi:10.1093/eurheartj/ehl053.]

This study provides information on doses of NSAID use that may be more variable and lower than those used in the Precision study.

Although multiple controls per case were used, the authors note that residual confounding is a potential issue. Factors like obesity, over-the-counter aspirin or NSAID use, smoking, income, or educational attainment) were not matched. The authors suggest that blood pressure increases or renal deterioration may have been more important possible confounders which were not adjusted for.

Conclusions included that all NSAIDs, including naproxen, were found to be associated with an increased risk of acute myocardial infarction. Risk of myocardial infarction with celecoxib was comparable to that of traditional NSAIDS and was lower than for the withdrawn rofecoxib (Vioxx).

3.2 Company reports

3.2.1 Pfizer Precision Study

[redacted]

- [redacted]
- [redacted]
- [redacted]

4.0 DISCUSSION AND CONCLUSIONS

4.1 Discussion

The Precision study [redacted]

The FDA's approach appears consistent with the accumulating evidence that cardiovascular disease risk may be equally associated with all non-aspirin NSAIDs, and appears appropriately conservative in in having the following sole contraindication: use during the perioperative period in the setting of coronary artery bypass graft (CABG) surgery. It is, therefore, proposed that New Zealand follow the FDA in datasheet contraindication and warning requirements regarding CV risk for non-aspirin NSAIDs.

A general contraindication for NSAIDs for all people with established CV disease is not warranted. Even in patients with established CV, the benefit of treatment with NSAIDs may, following a discussion about benefits and risks, outweigh the risk. Specific or particular contraindications may, however, be prudent for those with very high baseline risk. For example, patients in the perioperative period of CABG surgery; that is, those undergoing coronary artery surgery, could be considered at especially high risk for CV events.

In addition to a contraindication, a strong warning is appropriate as the risk includes death, and there are alternative treatments for moderate pain. The following Celecoxib datasheet warnings cover key elements to be taken into account when prescribing NSAIDs.

- The increased risk of serious CV thrombotic adverse events, myocardial infarction and stroke, which can be fatal.
- All NSAIDs, both COX-2 selective and non-selective may cause an increased risk of serious CV thrombotic events.
- This risk may increase with dose and duration of use.

  The relative increase of this risk appears to be similar in those with or without known CV disease or CV risk factors. However, patients with CV disease or CV risk factors may be at greater risk in terms of absolute incidence, due to their increased rate at baseline.

4.2 Conclusions

This paper proposes that the FDA's approach be followed, and that in addition to any product specific study information, the following general information regarding CV risk should be part of contraindications and warnings for celecoxib and other non-aspirin NSAIDs including ibuprofen:

> <u>contraindication</u> – patients undergoing treatment of perioperative pain in setting of coronary artery surgery.
>
> <u>warnings and precautions</u> -
>
> - Use of non-aspirin NSAIDs including Cox-2 inhibitors may cause an increased risk of serious adverse cardiovascular thrombotic events, myocardial infarction and stroke, which can be fatal.
> - All NSAIDs, both COX-2 selective and non-selective, may have a similar risk.
> - This risk may increase with dose and duration of use.

- The relative increase of this risk appears to be similar in those with or without known CV disease or CV risk factors. However, patients with CV disease or CV risk factors may be at greater risk in terms of absolute incidence, due to their increased rate at baseline.

5.0 ADVICE SOUGHT

The Committee is asked to advise whether:

- the proposed draft celecoxib datasheet contraindications and warning are appropriate
- contraindications and warning regarding cardiovascular disease risk for all non-aspirin NSAIDs, including COX-2 inhibitors, should be similar.

6.0 ANNEXES

1. FDA Drug Safety Communication: FDA strengthens warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes, 7 September 2015 - Page Last Updated: 11/16/2017.
2. Medsafe evaluation report; Celecoxib: relocating contraindication regarding established CVS disease to precautions, February 2018.
3. Nissen SE, Yeomans ND, Solomon DH, et al. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. NEJM 2016;375(26):2519-29.
4. Pepine C, Gurbel P. 2017. Cardiovascular safety of NSAIDs: additional insights after PRECISION and point of view. Clinical Cardiology 40: 1352-1356.
5. NHS Medicines Update regarding oral NSAIDs, 6 August 2017. www.ggcprescribing.org.uk/media/uploads/ps_extra/mu_extra_06_nsaids_2017.pdf
6. Sondergaard KB et al. Non-steroidal anti-inflammatory drug use is associated with increased risk of out-of-hospital cardiac arrest: a nationwide case-time-control study. European Heart Journal – Cardiovascular Pharmacotherapy (2017); 3:100-107. https://academic.oup.com/ehjcvp/article/3/2/100/2739709
7. Bally M, Dendukuri N, et al. Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data. BMJ 2017;357:j1909 http://dx.doi.org/10.1136/bmj.j1909

7.0 REFERENCES

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3. Medicines and Healthcare Products Regulatory Agency. High-dose ibuprofen (≥2400mg/day): small increase in cardiovascular risk. Drug safety update, Jun 2015. Available from https://www.gov.uk/drug-safety-update/high-dose-ibuprofen-2400mg-day-small-increase-in-cardiovascular-risk *
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6. Nissen SE, Yeomans ND, Solomon DH, et al. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. NEJM 2016;375(26):2519-29.
7. Pepine C, Gurbel P. 2017. Cardiovascular safety of NSAIDs: additional insights after PRECISION and point of view. Clinical Cardiology 40: 1352-1356.
8. Sondergaard KB et al. Non-steroidal anti-inflammatory drug use is associated with increased risk of out-of-hospital cardiac arrest: a nationwide case-time-control study. European Heart Journal – Cardiovascular Pharmacotherapy (2017); 3:100-107. https://academic.oup.com/ehjcvp/article/3/2/100/2739709

* reference not included as an Annex.