



Celecoxib: the “need to know” for safe prescribing

Celecoxib is a selective cyclo-oxygenase-2 (COX-2) inhibitor that has been fully subsidised without restriction, since 1 June, 2017. Celecoxib may be considered for the treatment of patients with acute pain, arthritic conditions or primary dysmenorrhoea as an alternative to the non-selective non-steroidal anti-inflammatory drugs (NSAIDs), e.g. naproxen and ibuprofen. A significant benefit of celecoxib is that it is associated with less risk of gastrointestinal bleeding compared to non-selective NSAIDs. Use of celecoxib is associated with an increase in cardiovascular risk, but this risk is similar to that associated with non-selective NSAIDs.

Celecoxib: now fully subsidised in New Zealand

Celecoxib capsules (100 and 200 mg) have been fully subsidised in New Zealand, without restriction, since June 1, 2017. Celecoxib is generally considered to be equally effective as naproxen, ibuprofen and diclofenac in reducing pain and inflammation.^{1,2}

Celecoxib can be considered for the treatment of patients with:³

- Acute pain
- Osteoarthritis
- Rheumatoid arthritis
- Ankylosing spondylitis
- Primary dysmenorrhoea

As with other NSAIDs, celecoxib is contraindicated in patients with NSAID hypersensitivity, e.g. those with asthma, urticaria, angioedema or rhinitis that is caused by a NSAID, including aspirin.³ Celecoxib is also contraindicated in patients with ischaemic heart disease, cerebrovascular disease, peripheral artery disease, mild to severe heart failure, active gastrointestinal ulceration or bleeding or inflammatory bowel disease.³ Caution is advised when considering the use of celecoxib in older patients and patients with reduced renal function, patients at risk of gastrointestinal bleeding and those taking medicines that may interact with NSAIDs, e.g. diuretics and ACE inhibitors.³ Celecoxib is associated with an increased risk of cardiovascular events, but this risk is similar to that of the non-selective NSAIDs (see: “The rise, fall and return of celecoxib”).

👁 Further information on the role of NSAIDs in the management of osteoarthritis is available from: “Managing patients with osteoarthritis: focus on the person rather than the pain”, www.bpac.org.nz/2018/osteoarthritis.aspx

COX inhibition explains the risks and benefits of celecoxib

NSAIDs produce their therapeutic effects, and adverse effects, by inhibiting the activity of COX-1 and/or COX-2 enzymes. The varying affinities of NSAIDs for COX-2, relative to COX-1, are thought to explain their differences in terms of gastrointestinal toxicity and cardiovascular risk.⁴ The inhibition of COX-1 results in reduced gastrointestinal mucosal protection and potentially adverse effects, such as gastrointestinal ulceration and bleeding. The inhibition of COX-2 prevents the production of the prostaglandins that mediate pain, inflammation and fever. However, as the selectivity for COX-2 inhibition increases, so does the risk of cardiovascular events.

The adverse effects of celecoxib

Celecoxib predominantly inhibits the COX-2 enzyme; referred to as selective COX-2 inhibition.* Celecoxib is therefore less likely to produce serious gastrointestinal adverse effects than the non-selective NSAIDs, e.g. naproxen and ibuprofen (see:

“Celecoxib has fewer gastrointestinal adverse effects than the non-selective NSAIDs”). However, as celecoxib does possess some degree of COX-1 inhibition at higher doses, the adverse effects associated with celecoxib are broadly similar to those of the non-selective NSAIDs, although their frequency may differ.⁴

Adverse effects of celecoxib include:³

- Gastrointestinal symptoms, ranging from dyspepsia to haemorrhage
- Increased blood pressure
- Headache
- Dizziness
- Sodium and fluid retention

See: nzf.org.nz/nzf_5498 for further details.

* Meloxicam is also a selective COX-2 inhibitor but it is subsidised with Special Authority approval only for patients with both haemophilia and haemophilic arthropathy that is inadequately controlled with other treatment options


👁 Further information on NSAIDs is available from: “Non-steroidal anti-inflammatory drugs (NSAIDs): Making safer treatment choices” www.bpac.org.nz/bpj/2013/october/nsaids.aspx




When to consider prescribing celecoxib

The clinical characteristics of the patient, their use of concurrent medicines and the pharmacology of the NSAIDs are used to determine if an NSAID is appropriate, and if so, which one should be prescribed. The factors to consider when assessing the patient are their risk of:

- Cardiovascular disease
- Gastrointestinal complications
- Chronic kidney disease (CKD)
- NSAID-related hypersensitivity
- Medicine interactions, e.g. avoiding the “triple whammy” of ACE inhibitors or angiotensin II receptor blockers, with diuretics and a NSAID

 Patients who are prescribed a NSAID should be warned against the concurrent use of over-the-counter products containing NSAIDs.

 The NZF interaction checker can be used to look for potentially significant interactions between NSAIDs and other medicines: http://nzf.org.nz/nzf_1

Celecoxib is associated with a cardiovascular risk similar to the non-selective NSAIDs

All NSAIDs, including naproxen, should be used cautiously in patients with elevated cardiovascular risk. This is because all NSAIDs (except aspirin) are associated with a dose-dependent, increased risk of cardiovascular events that can occur in the first weeks of treatment.¹³ The use of high daily doses of NSAIDs for 8–30 days has been shown to be associated with the greatest harms, e.g. celecoxib > 200 mg, diclofenac > 100 mg, ibuprofen > 1200 mg and naproxen > 750 mg.⁹ Patients with cardiovascular disease, especially those who have recently had a myocardial infarction or cardiac bypass surgery, are considered to be at the greatest risk of NSAID-related cardiovascular events, however, this risk is also present in patients without cardiovascular disease.¹³

This blanket caution on the use of NSAIDs with regard to cardiovascular risk is an update to previous guidance when it was advised that the use of relatively low-doses of naproxen or ibuprofen were not associated with an increased risk of cardiovascular events. However, recent evidence shows that the use of these NSAIDs is associated with a cardiovascular risk comparable to that of celecoxib (see: “The evidence from clinical trials”).¹⁰

The evidence from clinical trials: cardiovascular risk

The Prospective Randomised Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen (PRECISION) trial assessed the cardiovascular, gastrointestinal and renal

The rise, fall and return of celecoxib

Two selective COX-2 inhibitors, celecoxib (Celebrex) and rofecoxib (Vioxx), entered the international market in 1999 and both were widely prescribed following intensive promotion focusing on their decreased risk of gastrointestinal complications.⁶ Celecoxib and rofecoxib were approved for use in New Zealand, however, a decision on subsidising treatment was delayed until more was known about their safety.⁷ In 2003, the request for subsidy of celecoxib and rofecoxib was declined due to concerns about the cardiovascular safety of the selective COX-2 inhibitors.⁸ These concerns were subsequently confirmed and rofecoxib was withdrawn from the international market by the manufacturer in 2004.⁸ Celecoxib was allowed to remain on the market with a black box warning regarding the risk of cardiovascular events.⁶

In 2013, the safety data on the selective COX-2 inhibitors was reviewed.⁷ Several large, well-designed studies showed that the risk of cardiovascular events in patients taking moderate doses of celecoxib was similar to that of patients prescribed non-selective NSAIDs.^{9–11} In 2016, a proposal for subsidising celecoxib without restriction was considered and subsequently approved. Rofecoxib, however, remains unavailable as numerous studies have found that it is associated with an increased risk of cardiovascular events, relative to placebo and other NSAIDs.^{11, 12} Rofecoxib is thought to be associated with a higher risk of cardiovascular events than celecoxib because it is a more selective COX-2 inhibitor.

outcomes associated with celecoxib use (200 mg daily for most patients*), compared with naproxen (mean daily dose 852 mg) and ibuprofen (mean daily dose 2045 mg).¹⁰ Approximately 25,000 patients with osteoarthritis or rheumatoid arthritis were assigned to one of these medicines for a mean duration of 20 months.¹⁰ There was no significant difference in the adjusted composite number of cardiovascular deaths, non-fatal myocardial infarctions or non-fatal strokes in patients treated with any of the three medicines; 188 (2.3%) in patients taking celecoxib, 201 (2.5%) in patients taking naproxen and 218 (2.7%) in patients taking ibuprofen.¹⁰

* The dose of celecoxib was limited by regulatory restrictions to 200 mg daily for most patients, which may have provided a safety advantage for celecoxib by exposing patients to a lower equivalent dose compared to the other NSAIDs.¹⁰

A meta-analysis of eight randomised controlled trials or prospective cohort studies compared the association between myocardial infarction, stroke and cardiovascular death and the use of eight NSAIDs, including celecoxib.¹¹ Rofecoxib was found to be the only selective COX-2 inhibitor that was associated with an increased risk of cardiovascular events compared to placebo and the non-selective NSAIDs.¹¹

A recent population-based study of more than 440 000 individuals with over 61 000 cases of myocardial infarction found that the use of all NSAIDs was associated with an increased risk of myocardial infarction.⁹ The risk of myocardial infarction in patients taking celecoxib was comparable to that of patients taking non-selective NSAIDs and lower than those taking rofecoxib.⁹

Celecoxib has fewer gastrointestinal adverse effects than the non-selective NSAIDs

Celecoxib is recommended for patients at increased risk of gastrointestinal bleeding who require a NSAID.¹⁴ This is because celecoxib is associated with a lower risk of gastrointestinal bleeding than the non-selective NSAIDs.¹⁴ However, as some COX-1 inhibition is present, the use of celecoxib in patients with an elevated risk of gastrointestinal bleeding is not entirely without risk. Furthermore, the COX-2 enzyme may be involved in the healing of gastric lesions and therefore celecoxib, which inhibits COX-2, may prevent previously formed gastric lesions from healing.¹⁶ If the patient has a high risk of gastrointestinal complications, e.g. a history of NSAID-related gastrointestinal bleeding, a PPI should be concurrently prescribed.¹⁵ Risk factors for NSAID-induced gastrointestinal adverse effects include:⁵

- Age over 65 years
- A history of gastrointestinal bleeding
- Previous adverse reactions to NSAIDs
- The use of other medicines that increase the risk of bleeding, e.g. aspirin, warfarin, dabigatran, selective

serotonin reuptake inhibitors and corticosteroids

- Liver disease
- Chronic kidney disease
- Excess alcohol consumption

Patients should be advised to seek immediate medical attention if they vomit blood, pass dark stools or experience symptoms of anaemia. Patients with a high risk of gastrointestinal bleeding should be reviewed within the first month of treatment, including measurement of haemoglobin levels.⁵

The evidence from clinical trials: gastrointestinal risk

The Prospective Randomised Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen (PRECISION) trial found that over a mean period of 20 months there was a significantly lower risk of clinically significant gastrointestinal events or iron-deficiency anaemia of gastrointestinal origin in patients taking celecoxib (1.1%), compared with those taking naproxen (1.5%) or ibuprofen (1.6%).¹⁰ Another trial of 514 patients with arthritis, a history of gastrointestinal bleeding and high cardiovascular risk found that the use of celecoxib, aspirin and a PPI was associated with an incidence of recurrent upper gastrointestinal bleeding of 5.6% over 18 months, compared with 12.3% in patients prescribed naproxen, aspirin and a PPI.¹⁴

In patients with a history of NSAID-related gastrointestinal bleeding, the addition of a PPI to celecoxib reduces the risk of further gastrointestinal bleeding. In 441 patients with arthritis and a history of upper gastrointestinal bleeding, there were no cases of gastrointestinal bleeding over a 13-month period for patients who were co-prescribed celecoxib 200 mg, twice daily, and high-dose esomeprazole (equivalent to 20 mg omeprazole, twice daily) compared to 12 cases of gastrointestinal bleeding in those taking celecoxib and placebo.¹⁵

Celecoxib is associated with a similar risk of renal adverse events as the non-selective NSAIDs

Prostaglandins produced by the COX enzymes influence renal function through the regulation of vascular tone and blood flow.⁶ Inhibition of COX-1 is associated with decreased glomerular filtration.⁶ Inhibition of COX-2 is associated with retention of sodium.⁶ The use of non-selective NSAIDs or selective COX-2 inhibitors increases the risk of patients developing acute kidney injury (AKI) by approximately two-fold.¹⁷

The evidence from clinical trials: renal risk

A meta-analysis of five observational studies found that the use of ibuprofen and naproxen (doses not reported) was associated with a statistically significant increase in the risk of acute kidney injury (AKI).¹⁷ The use of celecoxib is also likely to increase the risk of patients developing AKI, although in this study a statistically

significant increase in risk was not detected.¹⁷ The Prospective Randomised Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen (PRECISION) trial found that the risk of adverse renal events was significantly lower in patients taking celecoxib (0.7% – 200 mg daily for most patients*), compared with patients taking ibuprofen (1.1% – mean daily dose 2045 mg), but not significantly lower than patients taking naproxen (0.9% – mean daily dose 852 mg).¹⁰

* The doses of celecoxib were limited by regulatory restrictions to 200 mg daily for most patients, which may have provided a safety advantage for celecoxib by exposing patients to a lower equivalent dose.¹⁰

Celecoxib is less likely to cause NSAID-hypersensitivity reactions than non-selective NSAIDs

A small number of patients who take NSAIDs will experience hypersensitivity reactions, e.g. aspirin-exacerbated respiratory disease and urticaria.^{3, 18} NSAID-induced bronchoconstriction occurs through inhibition of COX-1 and a subsequent imbalance between pro- and anti-inflammatory mediators.¹⁸ Celecoxib does not inhibit COX-1 as much as the non-selective NSAIDs and therefore is less likely to cause hypersensitivity reactions,^{18, 19} but it is still contraindicated in patients with a history of NSAID hypersensitivity; consider discussing use of celecoxib in these patients with an allergy specialist.

The evidence from clinical trials: hypersensitivity risk

A systematic review of studies assessing the tolerability of selective COX-2 inhibitors in patients with previous NSAID intolerance found that six out of 208 (3%) who took celecoxib displayed an adverse reaction.¹⁹ Another systematic review found that in patients with mild-to-moderate aspirin-exacerbated respiratory disease selective COX-2 inhibitors were safe.¹⁸

The clinical summary: celecoxib is preferred when there is a risk of gastrointestinal bleeding

Celecoxib is the recommended NSAID in patients at risk of gastrointestinal bleeding and is less likely to cause NSAID hypersensitivity reactions mediated by inhibition of COX-1, compared with the non-selective NSAIDs (Table 1). There appears to be no clinical difference between celecoxib and the non-selective NSAIDs in terms of analgesia and the risk of cardiovascular and renal adverse events is similar. As with other NSAIDs, the risk of adverse effects associated with celecoxib can be minimised by prescribing the lowest effective dose, for the shortest possible time, and reviewing the need for ongoing use at every consultation.

Table 1: Comparison of the benefits and risks of celecoxib compared to the non-selective NSAIDs.

Clinical effect	Celecoxib	Non-selective NSAIDs
Analgesia	=	=
Cardiovascular risk	=	=
Gastrointestinal complications	↓	↑
Renal adverse effects	=	=
NSAID-induced bronchoconstriction	↓	↑

↓ less risk, ↑ more risk, = equal risk (or benefit for analgesia)

Acknowledgement: Thank you to **Dr Rebecca Grainger**, Rheumatologist and Head of Department of Medicine, University of Otago, Wellington for expert review of this article. N.B. Expert reviewers are not responsible for the final content of the article.

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This article is available online at:

www.bpac.org.nz/2018/celecoxib.aspx