



Celecoxib Therapy and CYP2C9 Genotype

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Introduction

Celecoxib (brand name Celebrex) is a nonsteroidal anti-inflammatory drug (NSAID) that is used to manage osteoarthritis, rheumatoid arthritis, menstrual symptoms, and acute pain.

Celecoxib is a “COX-2 inhibitor.” The cyclooxygenase (COX) enzymes catalyze pathways that play a key role in the generation of the inflammatory response. Most NSAIDs inhibit both types of cyclooxygenase, COX-1 and COX-2, while celecoxib selectively inhibits COX-2.

Celecoxib is primarily metabolized by CYP2C9. Individuals who lack CYP2C9 activity (“CYP2C9 poor metabolizers”) have an increased exposure to celecoxib, and an increased risk of side effects.

Like all non-aspirin NSAIDs, celecoxib increases the risk of serious cardiovascular events, including myocardial infarction and stroke, and serious gastrointestinal (GI) adverse events such as bleeding, ulceration, and perforation.

The FDA-approved drug label states that in individuals “who are known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin), initiate treatment with half the lowest recommended dose” (Table 1)(1). Recommendations from the Clinical Pharmacogenetics Implementation Consortium (CPIC) include initiating celecoxib at 25–50% of the lowest recommended starting dose. Titrate dose upward to clinical effect or 25–50% of the maximum recommended dose with caution” (Table 2)(2).

Table 1. The FDA Celecoxib Dosage in CYP2C9 Poor Metabolizers (2020)

Phenotype	Dosage
Poor Metabolizers of CYP2C9 Substrates	In individuals who are known or suspected to be poor CYP2C9 metabolizers (namely, CYP2C9*3/*3 or *2/*3), based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin) administer celecoxib starting with half the lowest recommended dose. Alternative management should be considered in juvenile rheumatoid arthritis individuals identified to be CYP2C9 poor metabolizers.

This FDA table is adapted from (1).

Table 2. The CPIC Therapeutic Recommendations for Celecoxib (2020)

Phenotype ^a	Implication	Therapeutic recommendation	Classification of recommendation	Other considerations
CYP2C9 normal metabolizer (NM)	Normal metabolism	Initiate therapy with recommended starting dose. In accordance with the prescribing information, use the lowest effective dosage for shortest duration consistent with individual treatment goals.	Strong	
CYP2C9 intermediate metabolizer (IM) AS ^b of 1.5	Mildly reduced metabolism	Initiate therapy with recommended starting dose. In accordance with the prescribing information, use the lowest effective dosage for shortest duration consistent with individual treatment goals.	Moderate	IMs might have a higher-than-normal risk of adverse events especially in individuals with other factors affecting clearance of these drugs, such as hepatic impairment or advanced age.
CYP2C9 intermediate metabolizer AS of 1	Moderately reduced metabolism; higher plasma concentrations may increase probability of toxicities	Initiate therapy with lowest recommended starting dose. Titrate dose upward to clinical effect or maximum recommended dose with caution. In accordance with the prescribing information, use the lowest effective dosage for shortest duration consistent with individual treatment goals. Carefully monitor adverse events, such as blood pressure and kidney function during course of therapy.		
CYP2C9 poor metabolizer	Significantly reduced metabolism and prolonged half-life; higher plasma concentrations may increase probability and/ or severity of toxicities	Initiate therapy with 25–50% of the lowest recommended starting dose. Titrate dose upward to clinical effect or 25–50% of the maximum recommended dose with caution. In accordance with the prescribing information, use the lowest effective dosage for shortest duration consistent with individual treatment goals. Upward dose titration should not occur until after steady-state is reached (at least 8 days for celecoxib) Carefully monitor adverse events such as blood pressure and kidney function during course of therapy. Alternatively, consider an alternate therapy not metabolized by CYP2C9 or not significantly impacted by CYP2C9 genetic variants <i>in vivo</i> .	Moderate	Alternative therapies not primarily metabolized by CYP2C9 include aspirin, ketorolac ^c , naproxen, and sulindac. Selection of therapy will depend on individual treatment goals and risks for toxicity.

Table 2. continued from previous page.

Phenotype ^a	Implication	Therapeutic recommendation	Classification of recommendation	Other considerations
Indeterminate	N/A	No recommendation	No recommendation	N/A

AS, activity score; IMs, intermediate metabolizers; N/A, not applicable; PMs, poor metabolizers.

^a Separate drug-specific recommendation tables are available [online](#).

^b Activity score of a diplotype is based on assigned activity from 0 to 1 for each allele, see Table 3.

^c Approved for short-term use only.

This CPIC table is adapted from (2).

Drug Class: NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used to treat inflammation, fever, and pain. They are one of the most commonly used classes of medicine. Worldwide, it is estimated that more than 30 million people use NSAIDs daily (3).

More than 40 NSAIDs are licensed for use. Several NSAIDs (for example, aspirin, ibuprofen, and naproxen) are available over the counter, but stronger doses and other types of NSAIDs, such as celecoxib and piroxicam, are only available via prescription. It is thought that approximately 25% of the population has experienced NSAID-related side effects that require medical care (4).

The main action of NSAIDs is to inhibit cyclooxygenase (COX). Cyclooxygenase is the central enzyme in the synthesis of prostaglandins, prostacyclin, and thromboxanes from arachidonic acid. Prostaglandins can be protective (for example, protect the gastric mucosal lining and aid platelet aggregation) or inflammatory (for example, recruiting inflammatory white blood cells).

There are 2 main COX isoforms, and the safety and effectiveness of NSAIDs may be influenced by the degree they inhibit the 2 different forms. Cyclooxygenase-1 (COX-1) is a “housekeeping enzyme” that is expressed in most tissues. It protects the GI tract and induces platelet aggregation in response to injury. In contrast, COX-2 is often undetectable in tissues; however, the expression of COX-2 is increased during inflammation.

Most NSAIDs are non-selective COX inhibitors that inhibit both COX-1 and COX-2. There are exceptions, such as celecoxib, which is a selective COX-2 inhibitor that appears to be associated with fewer adverse GI events. However, GI adverse events still occur.

Approximately 25% of the exposed US population have experienced NSAID-related side effects that required medical care (4). Use of non-selective, non-aspirin NSAIDs may account for more than 30% of gastrointestinal bleeding cases in the US, resulting in 3,200 deaths per year in the 1990s (5). Overall mortality incidence rates are similar for non-selective NSAIDs and (48%) selective COX-2 inhibitors (47%) in older adults with arthritis (6). However, all non-aspirin NSAIDs have a boxed warning on the risk of serious GI and cardiovascular adverse events. For example:

“NSAIDs cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use.

NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events” (1).

Drug: Celecoxib

Celecoxib is an NSAID that is used to treat osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, painful menstruation, and acute pain. It is also used to reduce the number of colon and rectum polyps in individuals with familial adenomatous polyposis (1)

Celecoxib is a selective COX-2, but not COX-1, inhibitor that promotes the production of the gastric mucosal lining. Although celecoxib may be more gastroprotective than non-selective NSAIDs (7, 8, 9, 10), the use of celecoxib still increases the risks of gastrointestinal adverse events and the drug label has the same warning as for all NSAIDs, listing the gastric and cardiovascular risks (1).

The recommended dose in adults varies depending on the indication. For example, for osteoarthritis, the recommended dosage is 200 mg once daily or 100 mg twice daily, while for rheumatoid arthritis it is 100–200 mg twice daily. Because of the adverse events associated with any type of NSAID, the lowest effective dose of celecoxib should be used for the shortest duration consistent with the individual's treatment goals.

As for all NSAIDs, celecoxib is contraindicated in individuals with a known hypersensitivity or a history of asthma, urticaria, or other allergic-type reactions after taking aspirin or another NSAID. Celecoxib is also contraindicated to treat pain in the days following coronary heart disease surgery (NSAIDs cause an increased risk of myocardial infarction and stroke post-operatively), and celecoxib should be avoided by pregnant women starting at 30 weeks gestation (NSAID use in the third trimester causes an increased risk of premature closure of the fetal ductus arteriosus) (1).

Celecoxib is primarily metabolized by CYP2C9. Individuals with low CYP2C9 activity (“CYP2C9 poor metabolizers”) have a higher exposure to celecoxib (1).

There are insufficient studies of celecoxib use in pregnant women or during labor and delivery. Animal studies suggest celecoxib use during pregnancy or labor and delivery can lead to increased rates of embryo-fetal deaths, developmental abnormalities, pre- and post-implantation loss and stillbirth (1). Celecoxib is a prostaglandin-mediated NSAID and thus may delay or prevent rupture of ovarian follicles, leading to reversible infertility in some women (1).

Celecoxib has been approved for individuals 2 years and older with signs and symptoms of Juvenile Rheumatoid Arthritis. However, safety and efficacy have not been studied beyond 6 months in the pediatric population (1). Alternative therapies should be considered for pediatric individuals who are CYP2C9 poor metabolizers (1).

Elderly individuals are at a higher risk for NSAID-associated serious cardiovascular, GI, or renal adverse reactions; if celecoxib therapy is still strongly indicated despite the elevated risk, the FDA-approved drug label recommends initiating therapy at the low end of the dosing range with close monitoring for adverse effects (1).

Gene: CYP2C9

The cytochrome P450 superfamily (CYP450) is a large and diverse group of hepatic enzymes that form the major system for metabolizing lipids, hormones, toxins, and drugs. The CYP450 genes are very polymorphic and can result in reduced, absent, or increased enzyme activity.

The CYP2C9 protein metabolizes approximately 15% of clinically used drugs, and atypical metabolic activity caused by genetic variants in the *CYP2C9* gene can play a major role in adverse drug reactions (11, 12).

At least 16 different NSAIDs are metabolized, in part, by CYP2C9 (13). Celecoxib is extensively metabolized by CYP2C9 to form an inactive metabolite, with minor contributions from CYP3A4 (4).

The *CYP2C9* gene is highly polymorphic, with more than 60 known alleles. The *CYP2C9**1 allele is considered the wild-type allele when no variants are detected and is categorized by normal enzyme activity (14). Individuals who have 2 normal-function alleles (for example, *CYP2C9* *1/*1) are classified as “normal metabolizers”.

Two common allelic variants associated with reduced enzyme activity are *CYP2C9**2 (p.Arg144Cys) and *CYP2C9**3 (p.Ile359Leu). The *2 allele is more common in Caucasian (10–20%), than Asian (1–3%) or African (0–6%) populations. The *3 allele is less common (<10% in most populations) and is rare in African populations. In African-Americans and African populations, the *CYP2C9**8 (5–8%) allele is commonly seen followed by *5 and *11 (1.9–3.8%), which are rarely seen in other populations (<1%). (15, 16, 17, 18, 19) Importantly, it is the combination of both alleles that contributes to the overall metabolizer phenotype (Table 3).

Table 3. The CPIC Assignment of Likely *CYP2C9* Phenotype based on Genotype (2020)

Likely phenotype ^{a,b}	Activity score	Genotype	Examples of diplotype
Normal metabolizer	2	An individual who has 2 normal function alleles	*1/*1
Intermediate metabolizer	1.5 1	An individual who has one normal function allele plus one decreased function allele; OR one normal function allele plus one no function allele OR 2 decreased function alleles	*1/*2 *1/*3 *2/*2
Poor metabolizer	0.5 0	An individual who has one no function allele plus one decreased function allele; OR 2 no function alleles	*2/*3 *3/*3
Indeterminate	n/a	An individual who has allele combinations with uncertain ^c or unknown function alleles	*1/*7 *1/*10 *7/*10 *1/*58

Note: There are no known cases of *CYP2C9* ultrarapid metabolizers .

^a Assignment of allele function and associated citations can be found at the [CPIC website](#), also see *CYP2C9* Allele Definition Table and *CYP2C9* Allele Functionality Table in (2).

^b See the *CYP2C9* Frequency Table for population-specific allele and phenotype frequencies. (19)

^c Alleles with moderate to limited evidence on their effect on *CYP2C9* function.

This CPIC table has been adapted from (2).

Individuals with these variants have altered pharmacokinetics of several NSAIDs: celecoxib, flurbiprofen, ibuprofen, and tenoxicam (13, 20). This could potentially lead to dose recommendations based upon *CYP2C9* genotype and be used to identify individuals who are at increased risk of adverse events. However, pharmacogenetic testing has been limited to retrospective studies to identify the causes of an atypical response to NSAID (12).

Studies have found that *CYP2C9**3 is associated with an increased risk of bleeding associated with NSAID use (21, 22). In contrast, *CYP2C9**3 was found to be beneficial in a trial where celecoxib was given to prevent colorectal adenomas. High dose celecoxib had greater efficacy in preventing new adenomas than low-dose celecoxib, but only among individuals who had *CYP2C9**3 (23, 24).

The influence of other variant alleles, such as *CYP2C9**8 and *CYP2C9**11, on celecoxib levels in the plasma has not yet been evaluated. However, these 2 alleles are associated with the decreased function of the enzyme and hence the *CYP2C9* activity score is similar to other decreased function alleles of *CYP2C9* (for example, *2).

Coadministration of celecoxib with other drugs that alter *CYP2C9* activity may result in phenoconversion from one *CYP2C9* metabolizer phenotype to another. Some drugs, such as fluconazole, are known to inhibit *CYP2C9* and may increase the exposure and potential toxicity of celecoxib. Conversely, coadministration with *CYP2C9*

inducers like rifampin may lead to decreased efficacy of celecoxib. The FDA approved label for celecoxib advises that a dosage adjustment may be warranted when administered with CYP2C9 inhibitors or inducers. (1) Combination of NSAIDs—like celecoxib—and anticoagulants in CYP2C9 intermediate and poor metabolizers could increase the risk of gastrointestinal bleeding (25, 26).

Linking Gene Variation with Treatment Response

The FDA labeling for celecoxib recommends initiating treatment at half of the lowest recommended dose in known or suspected CYP2C9 poor metabolizers. This recommendation is supported by pharmacokinetic studies, which have shown individuals with decreased CYP2C9 activity have higher plasma levels of celecoxib (1, 27).

There is less data on how higher plasma levels of celecoxib influences the safety and efficacy of celecoxib. One study of 282 children treated with celecoxib after adenotonsillectomy found that children with a decreased function *CYP2C9* variant reported less pain than children without this variant (28).

Genetic Testing

Clinical *CYP2C9* genotyping tests are available that include a variable number of alleles. The NIH Genetic Testing Registry (GTR) displays genetic tests that are available for the *CYP2C9* gene and celecoxib response. In addition, variant *CYP2C9* alleles to be included in clinical genotyping assays have been recommended by the Association for Molecular Pathology (AMP). (29)

Individual results are typically reported as a diplotype, such as *CYP2C9* *1/*1, and may also include an interpretation with the predicted metabolizer phenotype (normal, intermediate, or poor). (Table 3).

Therapeutic Recommendations based on Genotype

This section contains excerpted¹ information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

2020 Statement from the US Food and Drug Administration (FDA): In adult patients who are known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin), initiate treatment with half of the lowest recommended dose.

In patients with juvenile rheumatoid arthritis (JRA) who are known or suspected to be poor CYP2C9 metabolizers, consider using alternative treatments.

[...]

Pharmacogenomics: CYP2C9 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity, such as those homozygous for the *CYP2C9**2 and *CYP2C9**3 polymorphisms. Limited data from 4 published reports that included a total of 8 subjects with the homozygous *CYP2C9**3/*3 genotype showed celecoxib systemic levels that were 3- to 7-fold higher in these subjects compared to subjects with *CYP2C9**1/*1 or *1/*3 genotypes. The pharmacokinetics of celecoxib have not been evaluated in subjects with other *CYP2C9* polymorphisms, such as *2, *5, *6, *9 and *11. It is estimated that the frequency of the homozygous *3/*3 genotype is 0.3% to 1% in various ethnic groups.

Please review the complete therapeutic recommendations that are located here: (1).

¹ The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labeled all formulations containing the generic drug.

2020 Statement from the Clinical Pharmacogenetics Implementation Consortium (CPIC):

Based on current evidence (Tables S1–S4), NMs and IMs with an AS of 1.5 are recommended to initiate therapy with the approved starting dose. Despite having mildly reduced metabolism, IMs with an AS of 1.5 do not exhibit significant increases in drug exposure relative to NMs (Figures S2–S4).

[...]

For IMs with an AS of 1, it is recommended to initiate NSAID therapy with the lowest recommended starting dose and titrate to clinical effect with close monitoring for adverse events, such as elevated blood pressure and kidney dysfunction during course of therapy.

[...]

Individuals with a CYP2C9 PM phenotype (AS of 0) are expected to have markedly reduced metabolism and are expected to exhibit a pronounced prolongation of drug half-life and increase in plasma concentrations, which may increase the probability and/or severity of toxicities. A meta-analysis of 7 small studies showed a ~ 400% increase of celecoxib exposure (ratio of means 4.17; 95% CI 1.85–9.37 *3/*3 vs. *1/*1; P = 0.005; Figure 1), whereas insufficient data exist for formal meta-analyses of ibuprofen, flurbiprofen, and lornoxicam. In this case, therapeutic recommendations involve dose reduction or alternative therapies, coupled with careful monitoring for adverse events, which are consistent with the US Food and Drug Administration (FDA) recommendations for celecoxib and flurbiprofen. It is recommended to initiate therapy with 25–50% of the lowest recommended starting dose (i.e., 50–75% dose reduction), and careful dose titration to clinical effect. Because drug half-life is significantly prolonged in these patients, upward dose titration should not occur until after steady-state is reached, taking into consideration the PM half-life for each drug; of course, dosing may be stopped or decreased due to toxicity at any time. Treatment with an alternative therapy could also be considered. This could include NSAIDs not primarily metabolized by CYP2C9 (such as aspirin, ketorolac (approved for short-term use only), metamizole, naproxen, sulindac, etoricoxib, parecoxib, or valdecoxib), or with pharmacokinetic parameters apparently not impacted by CYP2C9 genetic variants *in vivo* despite CYP2C9 metabolism *in vitro* (diclofenac, weak level of evidence, see Table S9). Some of these alternative drugs are not available worldwide (e.g., etoricoxib, metamizole, parecoxib, and valdecoxib) because of the elevated cardiovascular risk associated with COX-2-selective NSAIDs, and some have serious adverse events that need to be considered (e.g., diclofenac and liver toxicity, metamizole and agranulocytosis). Therefore, individual NSAIDs are not always therapeutically equivalent, and the selection of an alternative agent requires careful consideration of drug properties (e.g., half-life (Table S12), potency, metabolism, COX isoenzyme selectivity, and off-target effects) that may affect efficacy and safety.

Please review the complete therapeutic recommendations that are located here: (2).

Nomenclature for Selected CYP2C9 Alleles

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
CYP2C9*2	430C>T Arg144Cys	NM_000771.4:c.430C>T	NP_000762.2:p.Arg144Cys	rs1799853
CYP2C9*3	1075A>C Ile359Leu	NM_000771.4:c.1075A>C	NP_000762.2:p.Ile359Leu	rs1057910
CYP2C9*5	1080C>G Asp360Glu	NM_000771.4:c.1080C>G	NP_000762.2:p.Asp360Glu	rs28371686

Table continued from previous page.

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
CYP2C9*6	818delA Lys273Argfs	NM_000771.4:c.817delA	NP_000762.2:p.Lys273Argfs	rs9332131
CYP2C9*7	55C>A Leu 19Ile	NM_000771.4:c.55C>A	NP_000762.2:p.Leu19Ile	rs67807361
CYP2C9*8	449G>A Arg150His	NM_000771.4:c.449G>A	NP_000762.2:p.Arg150His	rs7900194
CYP2C9*9	10535A>G His251Arg	NM_000771.4:c.752A>G	NP_000762.2:p.His251Arg	rs2256871
CYP2C9*10	10598A>G Glu272Gly	NM_000771.4:c.815A>G	NP_000762.2:p.Glu272Gly	rs9332130
CYP2C9*11	1003C>T Arg335Trp	NM_000771.4:c.1003C>T	NP_000762.2:p.Arg335Trp	rs28371685
CYP2C9*58	1009C>A Pro337Thr	NM_000771.4:c.1009C>A	NP_000762.2:p.Pro337Thr	rs1274535931

Note: the normal “wild-type” allele is *CYP2C9*1* and is reported when no variant is detected.

Pharmacogenetic Allele Nomenclature: International Workgroup Recommendations for Test Result Reporting (30).

Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS).

Nomenclature and consensus based functional evidence of alleles for cytochrome P450 enzymes is available from Pharmacogene Variation (PharmVar) Consortium.

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Version history

To view the previous version (26 August 2016), please click [here](#).

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