

PRODUCT MONOGRAPH

PrCAMBIA®

Diclofenac potassium powder for oral solution
50 mg

Nonsteroidal Anti-Inflammatory Drug (NSAID)

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PrCAMBIA®

Diclofenac potassium powder for oral solution
50 mg

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
Oral	Powder for oral solution / 50 mg	Aspartame (equivalent to 25 mg phenylalanine), flavoring agents (anise and mint), glycerol behenate, mannitol, potassium bicarbonate, and saccharin sodium.

INDICATIONS AND CLINICAL USE

Adults

CAMBIA® (diclofenac potassium) is indicated for the acute treatment of migraine attacks with or without aura in adults 18 years and older.

Efficacy and safety of CAMBIA® beyond a single dose have not been studied.

CAMBIA® is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic, basilar, or ophthalmoplegic migraine. Safety and efficacy have not been established for cluster headache which is present in an older, predominantly male population.

Throughout this document, the term NSAIDs refers to both non-selective NSAIDs and selective COX-2 inhibitor NSAIDs, unless otherwise indicated.

For patients with an increased risk of developing Cardiovascular (CV) and/or Gastrointestinal (GI) adverse events, other management strategies that do NOT include the use of NSAIDs should be considered first (See CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Use of CAMBIA® should be limited to a single dose and for the shortest possible duration of treatment in order to minimize the potential risk for cardiovascular or gastrointestinal adverse events (See CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

CAMBIA®, as an NSAID, does NOT treat clinical disease or prevent its progression.

Geriatrics (> 65 years of age):

Safety and efficacy of CAMBIA® have not been studied in individuals over 65 years of age, and its use in this population is not recommended (See **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Pediatrics (< 18 years of age):

Safety and efficacy of CAMBIA® have not been studied in patients below the age of 18 years, and its use in this population is contraindicated (See **CONTRAINDICATIONS**).

CONTRAINDICATIONS

CAMBIA® is contraindicated in:

- known hypersensitivity to diclofenac potassium or to any of the components/excipients.
- the perioperative pain setting of coronary artery bypass graft (CABG) surgery. Although CAMBIA® has NOT been studied in this patient population, a selective COX-2 inhibitor NSAID studied in such a setting has led to an increased incidence of cardiovascular/thromboembolic events, deep surgical infections and sternal wound complications.
- the third trimester of pregnancy, because of risk of premature closure of the ductus arteriosus and prolonged parturition.
- women who are breastfeeding, because of the potential for serious adverse reactions in nursing infants.
- severe uncontrolled heart failure.
- history of asthma, urticaria, or allergic-type reactions after taking ASA or other NSAIDs (i.e. complete or partial syndrome of ASA-intolerance - rhinosinusitis, urticaria/angioedema, nasal polyps, asthma). Fatal anaphylactoid reactions have occurred in such individuals after taking NSAIDs. Individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse reaction. The potential for cross-reactivity between different NSAIDs must be kept in mind (See **WARNINGS AND PRECAUTIONS – Hypersensitivity Reactions - Anaphylactoid Reactions**).
- active gastric / duodenal / peptic ulcer, active GI bleeding.
- cerebrovascular bleeding or other bleeding disorders.
- inflammatory bowel disease.
- severe liver impairment or active liver disease.
- severe renal impairment (creatinine clearance <30 mL/min or 0.5 mL/sec) or deteriorating renal disease (individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed NSAIDs and must be monitored) (See **WARNINGS AND PRECAUTIONS - Renal**).

- known hyperkalemia (See **WARNINGS AND PRECAUTIONS - Renal - Fluid and Electrolyte Balance**).
- children and adolescents less than 18 years of age.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Risk of Cardiovascular Adverse Events:

Diclofenac is associated with an increased risk of cardiovascular adverse events (such as myocardial infarction, stroke or thrombotic events) that is comparable to COX-2 inhibitors and which can be fatal (See **WARNINGS AND PRECAUTIONS - Cardiovascular**). The risk may increase with duration of use. Meta-analyses of randomized clinical trials comparing several different NSAIDs suggest that diclofenac, particularly at higher doses, is associated with an increased risk of cardiovascular adverse events that is comparable to COX-2 inhibitors. Large population-based observational studies conducted in the general population also support these findings. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. To minimize the potential risk for an adverse CV event, CAMBIA® should be used for the shortest possible duration.

Treatment with CAMBIA® is not recommended in patients with pre-existing cardiovascular disease (congestive heart failure NYHA II-IV, ischemic heart disease, peripheral arterial disease), cerebrovascular disease, uncontrolled hypertension, and caution should be exercised in patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidemia, diabetes mellitus and smoking). These patients should be treated with CAMBIA® only after careful consideration.

Use of NSAIDs, such as CAMBIA® can promote sodium retention in a dose dependent manner, through a renal mechanism, which can result in increased blood pressure and/or exacerbation of congestive heart failure (See also **WARNINGS AND PRECAUTIONS - Renal - Fluid and Electrolyte Balance**).

Risk of Gastrointestinal (GI) Adverse Events

Use of NSAIDs, such as CAMBIA® is associated with an increased incidence of gastrointestinal adverse events (such as peptic/duodenal ulceration, perforation, obstruction and gastrointestinal bleeding) which can be fatal (See **WARNINGS AND PRECAUTIONS – Gastrointestinal**). Elderly patients are at a greater risk.

Risk in Pregnancy

CAMBIA® is contraindicated during the third trimester of pregnancy because of the risk of premature closure of the ductus arteriosus and prolonged parturition (See **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS – Pregnant Women**).

General

Frail or debilitated patients may tolerate side effects less well and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse event, the lowest effective dose should be used for the shortest possible duration.** As with other NSAIDs, caution should be used in the treatment of elderly patients who are more likely to be suffering from impaired renal, hepatic or cardiac function. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

CAMBIA® is NOT recommended for use with other NSAIDs, with the exception of low-dose ASA for cardiovascular prophylaxis, because of the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions (See **DRUG INTERACTIONS - Drug/Drug Interactions - Acetylsalicylic acid (ASA) or other NSAIDs**).

CAMBIA® should not be used concomitantly with diclofenac sodium containing products (e.g. VOLTAREN*) since both exist in plasma as the same active organic anion.

Interchangeability with Other Formulations of Diclofenac

Different formulations of diclofenac (e.g. diclofenac sodium or diclofenac potassium) may not be bioequivalent even if the milligram strength is the same. CAMBIA® cannot be replaced by any other diclofenac formulations, nor is it possible to convert dosing from any other formulation of diclofenac to CAMBIA®.

Carcinogenesis and Mutagenesis

(See **TOXICOLOGY**)

Cardiovascular

Diclofenac is associated with an increased incidence of cardiovascular (CV) adverse events (such as myocardial infarction, stroke or thrombotic events) similar to COX-2 inhibitors which can be fatal. The risk may increase with the dose and duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, transient ischemic attack).

Caution should be exercised in prescribing CAMBIA® to patients with risk factors for cardiovascular disease, cerebrovascular disease or renal disease, including but not limited to:

- **Hypertension**
- **Dyslipidemia / Hyperlipidemia**
- **Diabetes Mellitus**
- **Congestive Heart Failure (NYHA I)**
- **Coronary Artery Disease (Atherosclerosis)**
- **Peripheral Arterial Disease**
- **Smoking**
- **Creatinine Clearance < 60 mL/min or 1 mL/sec**

Use of NSAIDs, such as CAMBIA®, can lead to new hypertension or can worsen pre-existing hypertension, either of which may increase the risk of cardiovascular events as described above. Thus blood pressure should be monitored regularly. Consideration should be given to discontinuing CAMBIA® should hypertension either develop or worsen with its use.

Use of NSAIDs, such as CAMBIA®, can induce fluid retention and edema, and may exacerbate congestive heart failure through a renally-mediated mechanism (See **WARNINGS AND PRECAUTIONS - Renal - Fluid and Electrolyte Balance**).

For patients with a high risk of developing an adverse CV event, other management strategies that do NOT include the use of NSAIDs should be considered first. **To minimize the potential risk for an adverse CV event, the lowest effective dose should be used for the shortest possible duration.**

Endocrine and Metabolism

Corticosteroids:

CAMBIA® is NOT a substitute for corticosteroids. It does NOT treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids (See **DRUG INTERACTIONS - Drug-Drug Interactions - Glucocorticoids**).

Gastrointestinal (GI)

Serious GI toxicity (sometimes fatal), such as peptic / duodenal ulceration, inflammation, perforation, obstruction and gastrointestinal bleeding, can occur at any time, with or without warning symptoms, in patients treated with NSAIDs, such as CAMBIA®. Minor upper GI problems, such as dyspepsia, commonly occur at any time. Health care providers should remain alert for ulceration and bleeding in patients treated with CAMBIA®, even in the absence of previous GI tract symptoms. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration.** For high risk patients, alternate therapies that do not involve

NSAIDs should be considered (See **WARNINGS AND PRECAUTIONS - Special Populations - Geriatrics**).

Patients should be informed about the signs and/or symptoms of serious GI toxicity and instructed to discontinue using CAMBIA® and seek emergency medical attention if they experience any such symptoms. The utility of periodic laboratory monitoring has NOT been demonstrated, nor has it been adequately assessed. Most patients who develop a serious upper GI adverse event on NSAID therapy have no symptoms. Upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue, thus increasing the likelihood of developing a serious GI event at some time during the course of therapy. Even short-term therapy has its risks.

Caution should be taken if prescribing CAMBIA® to patients with a prior history of peptic / duodenal ulcer disease or gastrointestinal bleeding as these individuals have a greater than 10-fold higher risk for developing a GI bleed when taking a NSAID than patients with neither of these risk factors. Other risk factors for GI ulceration and bleeding include the following: *Helicobacter pylori* infection, increased age, prolonged use of NSAID therapy, excess alcohol intake, smoking, poor general health status or concomitant therapy with any of the following:

- Anti-coagulants (e.g. warfarin)
- Anti-platelet agents (e.g. ASA, clopidogrel)
- Oral corticosteroids (e.g. prednisone)
- Selective Serotonin Reuptake Inhibitors (SSRIs) (e.g. citalopram, fluoxetine, paroxetine, sertraline)

Genitourinary

Some NSAIDs are associated with persistent urinary symptoms (bladder pain, dysuria, and urinary frequency), hematuria or cystitis. The onset of these symptoms may occur at any time after the initiation of therapy with a NSAID. Should urinary symptoms occur, in the absence of an alternate explanation, treatment with CAMBIA® should be stopped to ascertain if symptoms disappear. This should be done before urological investigations or treatments are carried out.

Hematologic

NSAIDs inhibiting prostaglandin biosynthesis interfere with platelet function to varying degrees; patients who may be adversely affected by such an action, such as those on anti-coagulants or suffering from hemophilia or platelet disorders should be carefully observed when CAMBIA® is administered.

Anti-coagulants:

Numerous studies have shown that the concomitant use of NSAIDs and anti-coagulants increases the risk of bleeding. Concurrent therapy of CAMBIA® with warfarin requires close monitoring of the international normalized ratio (INR).

Even with therapeutic INR monitoring, increased bleeding may occur.

Anti-platelet Effects:

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike acetylsalicylic acid (ASA), their effect on platelet function is quantitatively less, or of shorter duration, and is reversible.

CAMBIA® and other NSAIDs have no proven efficacy as anti-platelet agents and should NOT be used as a substitute for ASA or other anti-platelet agents for prophylaxis of cardiovascular thromboembolic diseases. Anti-platelet therapies (e.g. ASA) should NOT be discontinued. There is some evidence that use of NSAIDs with ASA can markedly attenuate the cardioprotective effects of ASA (See **DRUG INTERACTIONS - Drug-Drug Interactions - Acetylsalicylic Acid (ASA) or other NSAIDs**).

Concomitant administration of CAMBIA® with low dose ASA increases the risk of GI ulceration and associated complications.

Blood dyscrasias:

Blood dyscrasias (such as neutropenia, leukopenia, thrombocytopenia, aplastic anemia and agranulocytosis) associated with the use of NSAIDs are rare, but could occur with severe consequences.

Anemia is sometimes seen in patients receiving NSAIDs, including CAMBIA®. This may be due to fluid retention, GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including CAMBIA®, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss.

Hepatic/Biliary/Pancreatic

As with other NSAIDs including CAMBIA®, borderline elevations of one or more liver enzyme tests (AST, ALT, alkaline phosphatase) may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy.

In clinical trials with diclofenac containing product, meaningful elevations (i.e., more than 3 × upper limit of normal (ULN)) of AST occurred in about 2% of approximately 5,700 patients at some time during treatment (ALT was not measured in all studies). In an open-label, controlled trial of 3,700 patients treated for 2–6 months with diclofenac containing product, patients were monitored at 8 weeks and 1,200 patients were monitored again at 24 weeks. Meaningful elevations of ALT and/or AST occurred in about 4% of the 3,700 patients and included marked elevations (>8 × ULN) in about 1% of the 3,700 patients. In this open-label study, a higher incidence of borderline (< 3 × ULN), moderate (3–8 × ULN), and marked (>8 × ULN) elevations of ALT or AST was observed in patients receiving diclofenac when compared to other NSAIDs. Almost all clinically relevant elevations in transaminases were detected before patients became symptomatic.

Post-market cases of drug-induced hepatotoxicity have been reported in the first month, and in some cases the first 2 months of diclofenac therapy, but can occur at any time during treatment with diclofenac. Post-marketing surveillance has reported cases of severe hepatic reactions, including liver necrosis, jaundice, fulminant hepatitis with and without jaundice, and liver failure. Some of these reported cases resulted in fatalities or liver transplantation.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with this drug.

To minimize the possibility that hepatic injury will become severe between transaminase measurements, physicians should inform patients of the warning signs and symptoms of hepatotoxicity and the appropriate action patients should take if these signs and symptoms appear. Physicians should exercise caution when prescribing CAMBIA® with concomitant drugs that are known to be potentially hepatotoxic (e.g. acetaminophen, certain antibiotics, antiepileptics).

CAMBIA® is contraindicated in severe liver impairment or active liver disease. If there is a need to prescribe this drug in the presence of impaired liver function, it must be done under strict observation (See **CONTRAINDICATIONS** and **ACTION AND CLINICAL PHARMACOLOGY-Hepatic Impairment**).

Caution is advised when using CAMBIA® in patients with hepatic porphyria, since CAMBIA® may trigger an attack.

Hypersensitivity Reactions

Anaphylactoid Reactions:

As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to CAMBIA®. In post-marketing experience, rare cases of anaphylactic/anaphylactoid reactions and angioedema have been reported in patients receiving CAMBIA®. CAMBIA® is contraindicated in patients with the ASA-triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking ASA or other NSAIDs (See **CONTRAINDICATIONS**).

ASA-Intolerance:

CAMBIA® is contraindicated in patients with complete or partial syndrome of ASA-intolerance. Fatal anaphylactoid reactions have occurred in such individuals. As well, individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse reaction (See **CONTRAINDICATIONS**).

Cross-sensitivity:

Patients sensitive to one NSAID may be sensitive to any of the other NSAIDs as well.

Serious skin reactions:

(See **WARNINGS AND PRECAUTIONS - Skin**)

Immune

(See **WARNINGS AND PRECAUTIONS - Infection- Aseptic Meningitis**)

Infection

CAMBIA®, as with other NSAIDs, may mask signs and symptoms of an underlying infectious disease.

Aseptic Meningitis:

Rarely, with some NSAIDs, the symptoms of aseptic meningitis (stiff neck, severe headaches, nausea and vomiting, fever or clouding of consciousness) have been observed. Patients with autoimmune disorders (systemic lupus erythematosus, mixed connective tissue diseases, etc.) seem to be pre-disposed. Therefore, in such patients, the health care provider must be vigilant to the development of this complication.

Neurologic

Some patients may experience drowsiness, dizziness, blurred vision, vertigo, tinnitus, hearing loss, insomnia or depression with the use of NSAIDs, such as CAMBIA®. If patients experience such adverse reaction(s), they should exercise caution in carrying out activities that require alertness.

Ophthalmologic

Blurred and/or diminished vision has been reported with the use of NSAIDs. If such symptoms develop, CAMBIA® should be discontinued and an ophthalmologic examination performed. Ophthalmologic examination should be carried out at periodic intervals in any patient receiving CAMBIA® for an extended period of time.

Sun exposure in patients using CAMBIA® might cause photosensitivity and vision changes. Patients should be advised to contact their physician for assessment and advice if this occurs.

Peri-Operative Considerations

(See **CONTRAINDICATIONS - Coronary Artery Bypass Graft Surgery**)

Phenylketonurics

Phenylketonurics patients should be informed that CAMBIA® contains aspartame equivalent to 25 mg phenylalanine per packet.

Psychiatric

(See **WARNINGS AND PRECAUTIONS – Neurologic**)

Renal

Long term administration of NSAIDs to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis, hematuria, low grade proteinuria and occasionally nephrotic syndrome.

During long-term therapy, kidney function should be monitored periodically (See **ACTION AND CLINICAL PHARMACOLOGY-Special Populations and Conditions-Renal Impairment**).

Renal impairment due to NSAID use is seen in patients with pre-renal conditions leading to reduction in renal blood flow or blood volume. Under these circumstances, renal prostaglandins help maintain renal perfusion and glomerular filtration rate (GFR). In these patients, administration of a NSAID may cause a reduction in prostaglandin synthesis leading to impaired renal function. Patients at greatest risk of this reaction are those with pre-existing renal impairment (GFR < 60 mL/min or 1 mL/s), dehydrated patients, patients on salt restricted diets, those with congestive heart failure, cirrhosis, liver dysfunction, taking angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, cyclosporin, diuretics, and those who are elderly. Serious or life-threatening renal failure has been reported in patients with normal or impaired renal function after short term therapy with NSAIDs. Even patients at risk who demonstrate the ability to tolerate a NSAID under stable conditions may decompensate during periods of added stress (e.g. dehydration due to gastroenteritis). Discontinuation of NSAIDs is usually followed by recovery to the pre-treatment state.

Caution should be used when initiating treatment with NSAIDs, such as CAMBIA®, in patients with considerable dehydration. Such patients should be rehydrated prior to initiation of therapy. Caution is also recommended in patients with pre-existing kidney disease.

Advanced Renal Disease:

CAMBIA® is contraindicated in patients with advanced renal disease (See **CONTRAINDICATIONS**).

Fluid and Electrolyte Balance:

Use of NSAIDs, such as CAMBIA®, can promote sodium retention in a dose-dependent manner, which can lead to fluid retention and edema, and consequences of increased blood pressure and exacerbation of congestive heart failure. Thus, caution should be exercised in prescribing CAMBIA® in patients with a history of congestive heart failure, compromised cardiac function, hypertension, increased age or other conditions predisposing to fluid retention (See **WARNINGS AND PRECAUTIONS - Cardiovascular**).

Use of NSAIDs, such as CAMBIA®, can increase the risk of hyperkalemia, especially in patients with diabetes mellitus, renal failure, increased age, or those receiving concomitant therapy with adrenergic blockers, angiotensin-converting enzyme inhibitors, angiotensin-II receptor antagonists, cyclosporin, or some diuretics.

Electrolytes should be monitored periodically (See **CONTRAINDICATIONS**).

Respiratory

ASA-induced asthma is an uncommon but very important indication of ASA and NSAID sensitivity. It occurs more frequently in patients with asthma who have nasal polyps.

Pre-existing asthma: In patients with asthma, seasonal allergic rhinitis, swelling of the nasal mucosa (i.e. nasal polyps), chronic obstructive pulmonary diseases or chronic infections of the respiratory tract (especially if linked to allergic rhinitis-like symptoms), reactions on NSAIDs like asthma exacerbations (so-called intolerance to analgesics / analgesics-asthma), Quincke's oedema or urticaria are more frequent than in other patients. Therefore, special precaution is recommended in such patients (readiness for emergency). This is applicable as well for patients who are allergic to other substances, e.g. with skin reactions, pruritus or urticaria.

Sexual Function/Reproduction

The use of CAMBIA®, as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. Therefore, in women who have difficulties conceiving, or who are undergoing investigation of infertility, withdrawal of CAMBIA® should be considered.

Skin

In rare cases, serious skin reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis and erythema multiforme have been associated with the use of some NSAIDs. Because the rate of these reactions is low, they have usually been noted during post-marketing surveillance in patients taking other medications also associated with the potential development of these serious skin reactions. Thus, causality is NOT clear. These reactions are potentially life threatening but may be reversible if the causative agent is discontinued and appropriate treatment instituted. Patients should be advised that if they experience a skin rash they should discontinue their NSAID and contact their physician for assessment and advice, including which additional therapies to discontinue.

Use of CAMBIA® may cause photosensitivity upon exposure to sunlight or UV light causing symptoms such as sunburn, skin rash, skin blisters, pruritus, erythema and discoloration.

Special Populations

Pregnant Women:

CAMBIA® is contraindicated for use during the third trimester of pregnancy because of risk of premature closure of the ductus arteriosus and the potential to prolong parturition (See CONTRAINDICATIONS and TOXICOLOGY).

CAMBIA® readily crosses the human placental barrier, thus CAMBIA® should not be prescribed during the first and second trimesters of pregnancy, unless the potential benefit to the mother outweighs the potential risk to the fetus. (See TOXICOLOGY)

Administration of diclofenac at the time of ovulation resulted in a long-lasting decrease in cervical mucus secretions in women with regular menstruation cycles which may affect fertility.

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or the embryo fetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation after use of a prostaglandin synthesis inhibitor in early pregnancy.

In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

The effects of CAMBIA® on labor and delivery in pregnant women are unknown. In rat studies, maternal exposure to NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, increased the incidence of dystocia, delayed parturition, and decreased pup survival.

Nursing Women:

CAMBIA® is excreted in human milk, and is contraindicated in nursing women (See **CONTRAINDICATIONS**).

Pediatrics (<18 years of age):

Safety and efficacy of CAMBIA® have not been studied in pediatric patients below the age of 18 years, and its use in this population is contraindicated (See **CONTRAINDICATIONS**).

Geriatrics (> 65 years of age):

Patients older than 65 years (referred to in this document as older or elderly) and frail or debilitated patients are more susceptible to a variety of adverse reactions from NSAIDs. The incidence of these adverse reactions increases with dose and duration of treatment. In addition, these patients are less tolerant to ulceration and bleeding. Most reports of fatal GI events are in this population. Older patients are also at risk of lower esophageal injury including ulceration and bleeding. For such patients, consideration should be given to a starting dose lower than the one usually recommended, with individual adjustment when necessary and under close supervision (See **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Gastrointestinal, dermatological, CNS and hepatic adverse reactions are the most commonly seen with diclofenac-containing products. The most severe gastrointestinal adverse reactions observed were ulceration and bleeding, while the most severe dermatological, albeit rare, reactions observed with diclofenac were erythema multiforme (Stevens-Johnson Syndrome and Lyell Syndrome). Fatalities have occurred on occasion, particularly in the elderly.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety of a single dose of CAMBIA® was evaluated within two placebo-controlled Phase III clinical trials. A total of 634 subjects were exposed to treatment with CAMBIA®. Of those subjects who ranged from 18 to 65 years of age, 543 (85.6%) were female.

The most commonly reported Adverse Events (AEs) in the CAMBIA® treatment group were in the system organ classes of gastrointestinal disorders, nervous system disorders and psychiatric disorders.

A summary of the most commonly reported treatment-emergent events is provided in Table 1.

Table 1: Treatment-Emergent Adverse Events with Incidences of > 1% by Treatment Group Following a Single Dose of CAMBIA®

System Organ Class MedDRA Preferred Term	Placebo n=646 (%)	CAMBIA® n=634 (%)
Gastrointestinal Disorders		
Abdominal pain upper	4 (0.6)	5 (0.8)
Dyspepsia	6 (0.9)	7 (1.1)
Nausea	18 (2.8)	25 (3.9)
Vomiting	5 (0.8)	8 (1.3)
Nervous System Disorders		
Dysgeusia	2 (0.3)	3 (0.5)
Psychiatric Disorders		
Insomnia	0 (0)	3 (0.5)
Restlessness	0 (0)	3 (0.5)

Less Common Clinical Trial Treatment--Emergent Adverse Events (<1%)

Gastrointestinal disorders: Abdominal distension, Abdominal pain, Glossitis, Hypoaesthesia oral, Paraesthesia oral, Stomach discomfort

General disorders and administration site conditions: Asthenia, Fatigue, Feeling abnormal, Irritability

Infections and infestations: Dysentery, Sinusitis

Injury, poisoning and procedural complications: Arthropod sting

Investigations: Heart rate increased

Musculoskeletal and connective tissue disorders: Musculoskeletal chest pain

Nervous system disorders: Ageusia, Headache, Hyperaesthesia, Paraesthesia, Tremor

Psychiatric disorders: Agitation, Anxiety, Confusional state, Déjà vu, Nervousness

Respiratory, thoracic and mediastinal disorders: Cough, Throat irritation

Skin and subcutaneous tissue disorders: Erythema, Hyperhidrosis, Urticaria

Vascular disorders: Flushing

Abnormal Hematologic and Clinical Chemistry Findings

(See **WARNINGS AND PRECAUTIONS** - *Blood dyscrasias*)

Post-Marketing Adverse Drug Reactions

The following adverse events not described elsewhere in the label have been identified during post-approval use of diclofenac-containing products including CAMBIA®. These reactions are reported voluntarily from a population of uncertain size, and it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Table 2: Post-Marketing Adverse Events for Diclofenac-containing Products

System Organ Class	Adverse Events
Blood and lymphatic system disorders	Agranulocytosis, Anaemia, Aplastic anaemia Eosinophilia, Hemolytic anaemia, Leukopenia, Lymphadenopathy, Pancytopenia, Thrombocytopenia
Cardiac disorders	Angina, Arrhythmia, Cardiac Arrest, Congestive heart failure, Myocardial infarction, Palpitation, Tachycardia
Ear and labyrinth disorders	Hearing impaired, Tinnitus, Vertigo
Eye disorders	Vision blurred, Conjunctivitis
Gastrointestinal disorders	Colitis, Colonic stenosis, Constipation, Eructation, Flatulence, Gastric ulcer, Gastritis, Gastrointestinal disorder, Gastrointestinal haemorrhage, Gastrointestinal ulcer, Glossitis, Gross bleeding/perforation, Haematochezia, Heartburn, Haematemesis, Melaena, Obstruction gastric, Oesophagitis, Pancreatitis, Peptic ulcer, Rectal haemorrhage, Stomatitis
General disorders and administration site conditions	Drug interaction, Death, Malaise, Multi-organ failure, Oedema, Product taste abnormal, Pyrexia
Hepatobiliary disorders	Hepatitis
Infections and infestations	Cystitis, Infection, Meningitis, Pneumonia, Sepsis, Septic shock
Investigations	Bleeding time increased, Heart rate decreased, Hepatic enzyme increased
Metabolism and nutrition disorders	Appetite disorder, Hyperglycaemia, Metabolic acidosis, Weight fluctuation
Nervous system disorders	Coma, Convulsion, Migraine, Syncope
Psychiatric disorders	Confusional state, Depression, Abnormal dreams, Hallucination
Renal and urinary disorders	Dysuria, Haematuria, Oliguria, Polyuria, Proteinuria, Renal impairment, Tubulointerstitial nephritis, Renal failure
Respiratory, thoracic and mediastinal disorders	Asthma, Dyspnoea, Epistaxis, Haemoptysis, Pulmonary hypertension, Respiratory depression
Skin and subcutaneous tissue disorders	Alopecia, Dermatitis exfoliative, Drug rash with eosinophilia and systemic symptoms, Ecchymosis, Photosensitivity reaction, Pruritus, Purpura, Rash, Stevens-Johnson syndrome, Toxic epidermal necrolysis
Vascular disorders	Hypertension, Hypotension, Vasculitis

DRUG INTERACTIONS

Drugs interacting with diclofenac are summarized below.

Overview

Effect of Other Drugs on the Metabolism of diclofenac: Co-prescribing diclofenac with potent CYP2C9 inhibitors could result in a significant increase in peak plasma concentrations and exposure to diclofenac due to inhibition of diclofenac metabolism. Diclofenac is metabolized predominantly by CYP2C9. Caution is recommended when co-prescribing CAMBIA® with potent CYP2C9 inhibitors, including sulfinpyrazone and voriconazole.

Drug-Drug Interactions

Acetaminophen

There may be an increased risk of adverse renal effects when administered concomitantly with NSAIDs. Physicians should caution their patients to avoid taking nonprescription acetaminophen-containing products while using CAMBIA®.

Acetylsalicylic acid (ASA/Aspirin) or other NSAIDs

The use of CAMBIA® in addition to any other NSAID, including over-the counter ones (such as ASA and diclofenac potassium) for analgesic and/or anti-inflammatory effects is NOT recommended because of the absence of any evidence demonstrating synergistic benefits and the potential risk for additive adverse reactions such as GI toxicity, including inflammation, bleeding and ulceration.

The exception is the use of low dose (81 mg daily) ASA for cardiovascular protection, when another NSAID is being used for its analgesic/anti-inflammatory effect, keeping in mind that combination NSAID therapy is associated with additive adverse reactions.

Some NSAIDs (e.g. diclofenac potassium) may interfere with the anti-platelet effects of low dose ASA, possibly by competing with ASA for access to the active site of cyclooxygenase-1.

CAMBIA® (diclofenac potassium) should not be used concomitantly with diclofenac sodium since both exist in plasma as the same active organic anion. Concomitant administration of diclofenac and other systemic NSAIDs or corticosteroids may increase the frequency of gastrointestinal adverse events.

Alcohol

There may be an increased risk of gastrointestinal side effects, including ulceration or hemorrhage, when administered concomitantly with NSAIDs.

Anti-coagulants

Concomitant administration of anti-coagulants (e.g. warfarin) with NSAIDs may increase risk for serious GI bleeding (See **WARNINGS AND PRECAUTIONS – Hematologic - Anti-coagulants**)

Anti-hypertensives

NSAIDs may diminish the anti-hypertensive effect of Angiotensin Converting Enzyme (ACE) inhibitors. Therefore, the combination should be administered with caution especially in the elderly.

Combinations of ACE inhibitors, angiotensin-II antagonists, or diuretics with NSAIDs might have an increased risk for acute renal failure and hyperkalemia. Blood pressure and renal function (including electrolytes) should be monitored more closely in this situation, as occasionally there can be a substantial increase in blood pressure (See **WARNINGS AND PRECAUTIONS – Renal**).

Anti-platelet Agents (including ASA)

There is an increased risk of bleeding, via inhibition of platelet function, when antiplatelet agents are combined with NSAIDs, including CAMBIA® (See **WARNINGS AND PRECAUTIONS – Hematologic - Anti-platelet Effects**).

Cyclosporine

CAMBIA®, like other NSAIDs, may affect renal prostaglandins and increase the toxicity of certain drugs. Therefore, concomitant therapy with CAMBIA® may increase cyclosporine's nephrotoxicity. Use caution when CAMBIA® is administered concomitantly with cyclosporine.

Digoxin

Diclofenac, like other NSAIDs, may affect renal prostaglandins and increase plasma concentration of digoxin. Use caution when CAMBIA® is administered, and, monitoring of serum digoxin level is also recommended.

Diuretics

Clinical studies as well as post-marketing observations have shown that NSAIDs can reduce the effect of diuretics (See **WARNINGS AND PRECAUTIONS – Renal**).

Glucocorticoids

Some studies have shown that the concomitant use of NSAIDs and oral glucocorticoids increases the risk of GI adverse events such as ulceration and bleeding. This is especially the case in older (> 65 years of age) individuals.

Lithium

NSAIDs have produced 15% elevations of plasma lithium levels and a 20 % reduction in renal lithium clearance. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. When CAMBIA® and lithium are administered concurrently, observe patients carefully for signs of lithium toxicity.

Methotrexate

NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This indicates that NSAIDs may enhance the toxicity of methotrexate. Caution should be exercised when CAMBIA® is administered less than 24 hours before or after treatment with methotrexate.

Oral Hypoglycemics

There are isolated reports of hyperglycemia and hypoglycemia when the drugs are taken together which necessitated a change in oral hypoglycemic drug dose.

Phenytoin

When using phenytoin concomitantly with diclofenac, monitoring of phenytoin plasma concentrations is recommended due to an expected increase in exposure to phenytoin.

Probenecid

Probenecid may decrease the excretion and increase serum concentrations of NSAIDs possibly enhancing effectiveness and/or increasing potential for toxicity. Concurrent therapy of NSAIDs with probenecid requires close monitoring to be certain that no change in dosage is necessary.

Quinolone antibacterials

There have been isolated reports of convulsions which may have been due to concomitant use of quinolones and NSAIDs.

Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

Concomitant administration of NSAIDs, including CAMBIA®, and SSRIs and SNRIs may increase the risk of gastrointestinal ulceration and bleeding (See **WARNINGS AND PRECAUTIONS - Gastrointestinal**).

Tacrolimus

Nephrotoxicity of tacrolimus may be increased because of the effect of NSAIDs on renal prostaglandins. Caution is recommended when co-prescribing CAMBIA® with tacrolimus.

Drug-Food Interactions

Whereas taking CAMBIA® with a meal may cause a delay in total absorption as compared to taking CAMBIA® on an empty stomach, food may reduce the risk of gastro-intestinal side effects. A high fat meal may be associated with decreased peak plasma levels (C_{max}) of diclofenac (See **ACTION AND CLINICAL PHARMACOLOGY; Pharmacokinetics, Absorption**).

Drug-Herb Interactions

Interaction of CAMBIA® with herbal products has not been studied.

Drug-Laboratory Test Interactions

Diclofenac increases platelet aggregation time but does not affect bleeding time, plasma thrombin clotting time, plasma fibrinogen, or factors V and VII to XII. Statistically significant changes in prothrombin and partial thromboplastin times have been reported in normal volunteers. The mean changes were observed to be less than 1 second in both instances. Persistently abnormal or worsening renal, hepatic or hematological test values should be followed up carefully since they may be related to CAMBIA® therapy.

Drug Lifestyle Interaction

Patients experiencing visual disturbances, dizziness, vertigo, somnolence or other central nervous system disturbances while taking CAMBIA® should refrain from driving or using machines (See **ADVERSE REACTIONS**).

DOSAGE AND ADMINISTRATION

Dosing Considerations

CAMBIA® is recommended only for the acute treatment of migraine attacks. CAMBIA® should not be used prophylactically.

Controlled trials have not studied a second dose if the initial dose is ineffective. The safety of treating more than one headache in a 30-day period has not been studied.

Pregnancy: CAMBIA® is contraindicated for use during the third trimester of pregnancy. CAMBIA® should not be prescribed during the first and second trimesters of pregnancy, unless the potential benefit to the mother outweighs the potential risk to the fetus (See **WARNINGS AND PRECAUTIONS – Special Populations**).

Pediatrics: CAMBIA® is contraindicated in pediatric patients below the age of 18 years.

Geriatrics: Care should be taken when using CAMBIA® in the elderly, frail and debilitated. Elderly patients are at increased risk for serious GI adverse events and are more likely to have decreased renal function (See **WARNINGS AND PRECAUTIONS-Special Populations - Geriatrics**).

Renal Impairment: CAMBIA® is not recommended in patients with renal impairment (See **ACTION AND CLINICAL PHARMACOLOGY-Renal Impairment**) and is contraindicated in patients with severe renal impairment (See **CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS– Renal**).

Hepatic Impairment: CAMBIA® is not recommended in patients with hepatic impairment (See **ACTION AND CLINICAL PHARMACOLOGY-Hepatic Impairment**) and is contraindicated in patients with severe hepatic impairment function (See **CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS - Hepatic/ Biliary/ Pancreatic**).

Migraine symptoms: Caution is recommended when prescribing CAMBIA® when vomiting is a significant component of the migraine attack.

Taking CAMBIA® with a meal may cause a delay in efficacy (See **Drug-Food Interactions**).

Recommended Dose and Dosage Adjustment

Only one single dose sachet of CAMBIA® (diclofenac potassium) is to be taken for the acute treatment of a migraine attack. The safety and efficacy of a second dose have not been studied.

Administration

Diclofenac potassium powder for oral solution:

Empty the contents of one individual dose sachet into a cup containing 30 to 60 mL (1 to 2 ounce) of water; mix well. Ensure that the powder is completely dissolved before drinking. Drink the water-powder mixture immediately after re-constitution. Do NOT use liquids other than water.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Symptoms following acute diclofenac overdose are usually limited to lethargy, drowsiness, dizziness, tinnitus or convulsions, nausea, vomiting, epigastric pain and diarrhea, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

Therapeutic measures

Management of acute poisoning with NSAIDs, including CAMBIA®, essentially consists of supportive measures and symptomatic treatment. Supportive measures and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal disorder, and respiratory depression. Special measures such as forced diuresis, dialysis or haemoperfusion are probably of no help in eliminating NSAIDs, including CAMBIA®, due to the high protein binding and extensive metabolism. Activated charcoal may be considered after ingestion of a potentially toxic overdose, and gastric decontamination (e.g. vomiting, gastric lavage) after ingestion of a potentially life threatening overdose.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Like other non-selective NSAIDs, diclofenac exerts its principal effect by inhibiting the cyclooxygenase (COX) enzymes COX-1 and COX-2. This inhibition leads to decreases in prostaglandin production; prostaglandins play a major role in causing inflammation and pain.

Pharmacodynamics

Diclofenac is a non-selective NSAID possessing analgesic, antipyretic, and anti-inflammatory properties. The mechanism responsible for these pharmacological effects is the inhibition of prostaglandin synthesis. Diclofenac is a potent inhibitor of cyclo-oxygenase (COX) enzymes COX-1 and COX-2 *in vitro* and *in vivo* which decreases the synthesis of prostaglandins, prostacyclin, and thromboxane products. Prostaglandins play a major role in causing inflammation, pain, and fever, and adaptive and protective reactions in many organs and (inflamed) tissues.

Pharmacokinetics

Absorption:

Diclofenac is almost completely absorbed after oral administration. However, due to first-pass metabolism, only about 50 to 60% of the absorbed dose is systemically available in the unchanged form.

In fasted normal healthy subjects, significantly measurable plasma levels were observed within 5 minutes of dosing with CAMBIA®. Time to reach maximum plasma levels (T_{max}) were achieved after approximately 15 minutes (range: 10 to 40 minutes) in fasting conditions, while under fed conditions T_{max} was approximately 10 minutes (range: 5 minutes to 4 hours). Mean area under the plasma curve (AUC) values for diclofenac were 1254.6 and 1084.2 ng*hr/mL for CAMBIA® under fasting and fed conditions, respectively. Mean maximum concentration (C_{max}) values for diclofenac were 1618.3 and 505.5 ng/mL for CAMBIA® under fasting and fed conditions, respectively. A high fat meal had no significant effect on the extent of diclofenac absorption; however, it caused a reduction in the C_{max} of approximately 70%.

Distribution:

The apparent volume of distribution of diclofenac is 0.12 to 0.17 L/kg. Diclofenac is more than 99% bound to human serum proteins, primarily to albumin.

Metabolism:

Orally administered diclofenac is subject to first-pass metabolism and only 50-60% of the drug reaches the systemic circulation in the unchanged form.

Five major hydroxylated metabolites have been identified in human plasma and urine. The metabolites include 3'-hydroxy, 4'-hydroxy, 5-hydroxy, 4',5-dihydroxy-, and 3'-hydroxy-4'-methoxy diclofenac. The major diclofenac metabolite, 4'-hydroxy diclofenac, has very weak pharmacologic activity. The formation of 4'-hydroxy diclofenac is primarily mediated by CPY2C9. Both diclofenac and its oxidative metabolites undergo glucuronidation or sulfation followed by biliary excretion. Acyl glucuronidation mediated by UGT2B7 and oxidation mediated by CPY2C8 may also play a role in diclofenac metabolism. CYP3A4 is responsible for the formation of minor metabolites, 5-hydroxy and 3'-hydroxy diclofenac. In patients with renal impairment, peak concentrations of metabolites 4'-hydroxy and 5-hydroxyl diclofenac were respectively approximately 50% and 4% of the parent compound after single oral dosing

compared to 27% and 1% in normal healthy subjects.

Excretion:

Plasma clearance of diclofenac is 263 ± 56 mL/min. Diclofenac is eliminated principally through hepatic metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites. About 1% of an oral dose is excreted unchanged in urine. Approximately 65% of the dose is excreted in the urine and approximately 35% in the bile as conjugates of unchanged diclofenac plus metabolites.

The terminal half-life of unchanged diclofenac is approximately 2 hours.

Special Populations and Conditions

Hepatic Impairment:

There is no information available regarding the use of CAMBIA® in patients with hepatic impairment.

Since the liver metabolizes almost 100% of diclofenac, patients with any degree of hepatic impairment should be considered for treatment with CAMBIA® only if the benefits outweigh the risks (See **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS-Hepatic/Biliary/Pancreatic**).

Renal Impairment:

There is no information available regarding the use of CAMBIA® in patients with renal impairment.

Caution is advised while administering CAMBIA® to patients with any degree of impaired kidney function (See **WARNINGS AND PRECAUTIONS-Renal**). CAMBIA® is contraindicated in patients with severely impaired or deteriorating renal function (creatinine clearance < 30 mL/min (0.5 mL/sec)) (See **CONTRAINDICATIONS**).

STORAGE AND STABILITY

Store at 15-30°C (59°F-86°F).

DOSAGE FORMS, COMPOSITION AND PACKAGING

CAMBIA® 50 mg (diclofenac potassium powder for oral solution) is supplied as one or more sets of three perforated co-joined individual dose sachets. Each individual dose sachet is designed to deliver a dose of 50 mg diclofenac potassium when mixed in water.

CAMBIA® is a white to off-white, buffered, flavored powder for oral solution packaged in individual dose sachets.

Non-medicinal ingredients in CAMBIA® include: Aspartame (equivalent to 25 mg phenylalanine), flavoring agents (anise and mint), glycerol behenate, mannitol, potassium bicarbonate, and saccharin sodium.

Boxes of three (3) CAMBIA® Individual dose Sachets

Boxes of nine (9) CAMBIA® Individual dose Sachets

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Diclofenac Potassium

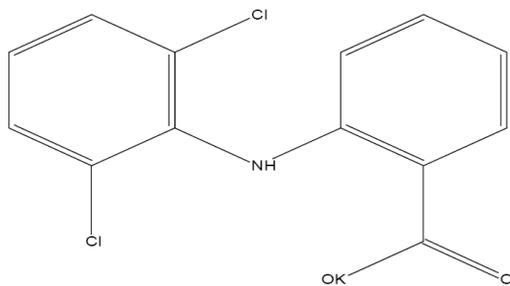
Chemical name: Potassium-[o-[(2,6-dichlorophenyl)-amino]-phenyl]-acetate.

Molecular formula and molecular mass:

Molecular weight: 334.25

Molecular formula: $C_{14}H_{10}Cl_2NKO_2$

Structural formula:



Physicochemical properties: Diclofenac potassium is a white to off-white powder. At 25°C diclofenac potassium is 5% soluble in water (pH 7.7). It is practically insoluble in aqueous acidic solutions. The addition of the buffering agent potassium bicarbonate at 1.1%, allows diclofenac-K to dissolve in its ionized form in tap water at a pH of 7.5.

CLINICAL TRIALS

The efficacy of CAMBIA® in the acute treatment of migraine headache has been demonstrated in a randomized, double-blind, placebo-controlled, parallel-group trial. Patients enrolled in the trial were predominantly female (85%) and white (80%), with a mean age of 40 years (range: 18 to 65). A total of 343 migraine patients were treated with CAMBIA® in the study.

Subjects treated one migraine attack with one single dose of either CAMBIA® or placebo. Patients treated a migraine of moderate to severe pain.

The percentage of subjects who were pain free 2 hours later was assessed. Associated symptoms of nausea, photophobia, and phonophobia were also evaluated 2 hours post-dose. Headache response (defined as a reduction in headache severity from moderate or severe pain to mild or no pain) 2 hours after treatment was also recorded.

Study results

The percentage of subjects achieving pain freedom 2 hours after treatment was significantly greater ($p < 0.001$) in patients who received CAMBIA® (25%) compared with those who received placebo (10%). In addition, there was a significant decreased incidence of nausea, photophobia and phonophobia in patients treated with CAMBIA® as compared to placebo 2 hours after treatment. Headache response 2 hours post-dose was also significantly superior in patients who received CAMBIA® compared to those who received placebo.

Additionally, it was demonstrated that CAMBIA® had a rapid onset of action (within 30 minutes of dosing). The efficacy and safety of CAMBIA® was unaffected by age or gender of the patient.

DETAILED PHARMACOLOGY

Diclofenac is a phenyl-acetic acid derivative possessing anti-inflammatory and analgesic activities as shown in various pharmacological models. The mechanism responsible for these pharmacological effects is mainly in the inhibition of prostaglandin synthesis.

The anti-inflammatory potency of diclofenac potassium was assessed by testing inhibition of paw edema (carrageenan solution) in rats.

The antinociceptive effect of diclofenac potassium was assessed by the writhing test in mice.

TOXICOLOGY

Since the same active, diclofenac, is absorbed from the potassium and sodium salts, toxicological finding with diclofenac sodium are representative of systemic toxicities with diclofenac potassium.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term carcinogenicity studies in rats given diclofenac sodium up to 2 mg/kg/day (less than the recommended human dose [RHD] of 50 mg/day on a body surface area [mg/m^2] basis) have revealed no significant increases in tumor incidence. There was a slight increase in benign mammary fibroadenomas in mid-dose treated (0.5 mg/kg/day or 3 mg/m^2 /day) female rats (high-dose females had excessive mortality), but the increase was not significant for this common rat tumor. A 2-year carcinogenicity study conducted in mice employing diclofenac sodium at doses up to 0.3 mg/kg/day (less than the RHD on a mg/m^2 basis) in males and 1 mg/kg/day (less than the RHD on a mg/m^2 basis) in females did not reveal any oncogenic potential.

Diclofenac sodium was not genotoxic in *in vitro* (reverse mutation in bacteria [Ames], mouse lymphoma thymidine kinase) or in *in vivo* (including dominant lethal and male germinal epithelial chromosomal aberration in Chinese hamster) assays.

Diclofenac sodium administered to male and female rats at 4 mg/kg/day (less than the RHD on a mg/m^2 basis) did not affect fertility.

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PART III: CONSUMER INFORMATION**PR** CAMBIA®

(diclofenac potassium powder for oral solution)

This leaflet is part III of a three-part "Product Monograph" published when CAMBIA® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about CAMBIA®.

Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION**What the medication is used for:**

Your doctor has prescribed CAMBIA® for you to treat a migraine attack. CAMBIA® is only for use in adults 18 years and older.

Use only a single dose of CAMBIA® to treat one migraine attack.

Do not use CAMBIA® continuously to prevent or reduce the number of migraines you experience. CAMBIA® should not be used to relieve pain other than that associated with migraine.

What it does:

CAMBIA® is a nonsteroidal anti-inflammatory drug (NSAID), and can reduce the chemicals prostaglandins produced by your body, which cause pain and swelling.

CAMBIA® does NOT prevent migraines or cure your condition.

When it should not be used:

DO NOT TAKE CAMBIA® if you have any of the following medical conditions:

- Heart bypass surgery (planning to have or recently had)
- Severe, uncontrolled heart failure
- Bleeding in the brain or other bleeding disorders
- Currently or planning to become pregnant
- Currently breastfeeding (or planning to breastfeed)
- Allergy to diclofenac or ASA (Acetylsalicylic Acid) or other NSAIDs (Nonsteroidal Anti-Inflammatory Drugs) or any of the non-medical ingredients in CAMBIA®
- Ulcer (active)
- Bleeding from the stomach or gut (active)
- Inflammatory bowel disease (Crohn's Disease or Ulcerative Colitis)
- Liver disease (active or severe)
- Kidney disease (severe or worsening)
- Have high potassium in the blood

Patients who took a drug in the same class as CAMBIA® after heart surgery, such as coronary artery bypass grafting were more likely to have heart attack, stroke, blood clots in the legs or lungs, and infections or other complications than those who did NOT take that drug.

CAMBIA® should NOT be used in patients under 18 years of age.

What the medicinal ingredient is:

diclofenac potassium

What the non-medical ingredients are:

Aspartame (equivalent to 25 mg phenylalanine), flavoring agents (anise and mint), glycerol behenate, mannitol, potassium bicarbonate, and saccharin sodium

What dosage forms it comes in:

Each individual sachet of CAMBIA® contains 50 mg of diclofenac potassium powder, to add to water for oral use.

WARNINGS AND PRECAUTIONS**Serious Warnings and Precautions**

CAMBIA® can increase your risk of fatal heart attack, angina, heart failure, high blood pressure, stroke or mini-stroke. The risk may be greater if you had any of these conditions or you are at risk for getting them. The risk may increase with continued use of CAMBIA®.

CAMBIA® can cause fatal bleeding and ulcers in the stomach or gut at any time during treatment. Elderly patients are at a greater risk.

CAMBIA® is not for use during the last 3 months of pregnancy because it may harm the baby and cause complications during delivery.

If you have any of the above medical conditions, see your doctor to discuss treatment options other than CAMBIA®.

BEFORE you use CAMBIA® talk to your doctor or pharmacist if you have, or previously had:

- Congestive heart failure
- Heart attack or Angina
- Stroke or Mini-stroke
- High blood pressure
- High cholesterol
- Diabetes mellitus or on a low sugar diet
- Atherosclerosis (vascular disease)
- Poor circulation to your extremities
- Smoker or ex-smoker
- Kidney disease or urine problems
- Previous ulcer or bleeding from the stomach or gut
- Previous bleeding in the brain
- Bleeding problems
- Family history of allergy to NSAIDs, such as acetylsalicylic acid (ASA), celecoxib, diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, rofecoxib, sulindac, tenoxicam, tiaprofenic acid, tolmetin, or valdecoxib (NOT a complete list)
- Family history of asthma, nasal polyps, long-term swelling of the sinus (chronic sinusitis) or hives
- Family history of allergy to sulfonamide drugs
- Any other medical problem such as alcohol abuse

- A history of stomach upset

Also, before taking this medication, tell your doctor if you are planning to get pregnant. CAMBIA® is not recommended during pregnancy because it may harm the baby.

While taking this medication:

- tell any other doctor, dentist, pharmacist or other health care professional that you see, that you are taking this medication, especially if you are planning to have heart surgery;
- do NOT drink alcoholic beverages while taking this medication because you would be more likely to develop stomach problems;
- fertility may be decreased. The use of CAMBIA® is not recommended in women trying to get pregnant. In women who have difficulty conceiving, stopping CAMBIA® should be considered.

Phenylketonurics: Contains Aspartame

- Voriconazole
- Warfarin-Type Anticoagulants

Your doctor may prescribe low dose ASA (acetylsalicylic acid) as a blood thinner to reduce your risk of having a heart attack or stroke while you are taking CAMBIA®. Take only the amount of ASA prescribed by your doctor. You are more likely to upset or damage your stomach if you take both CAMBIA® and ASA than if you took CAMBIA® alone.

PROPER USE OF THIS MEDICATION

Usual dose for adults over 18 years of age:

One individual dose sachet at any time during a migraine attack.

Directions for use:

Open individual dose sachet only when ready to use. Empty the contents of one individual dose sachet into 30 to 60 mL (1 to 2 ounces) of water. Do not use liquids other than water. Mix to ensure that the powder is completely dissolved. Drink the water-powder mixture immediately after mixing.

Taking CAMBIA® with a meal may delay pain relief; however food may reduce possible stomach and intestinal side-effects.

Take CAMBIA® only as directed by your doctor. **Do NOT take more of it, do NOT take it more often and do NOT take it for a longer period of time than your doctor recommended. If possible, you should take this medication for the shortest time period.**

Taking too much CAMBIA® may increase your chances of unwanted and sometimes dangerous side effects, especially if you are elderly, have other diseases or take other medications.

Repeated use of CAMBIA® can cause headaches. See your doctor regularly to discuss whether this medicine is working for you and if it is causing you any unwanted effects.

This medication has been prescribed specifically for you. Do NOT give it to anyone else. It may harm them, even if their symptoms seem to be similar to yours.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Center immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

CAMBIA® may cause some side effects, especially when used for a long time or in large doses. When these side effects occur, you may require medical attention. Report all symptoms or side effects to your doctor.

CAMBIA® may cause you to become drowsy or tired. Be careful about driving or participating in activities that require you to be

INTERACTIONS WITH THIS MEDICATION

Talk to your doctor and pharmacist if you are taking any other medication (prescription or non-prescription); such as any of the medications listed below (this is NOT a complete list).

Drugs that may interact with CAMBIA® include:

- Acetaminophen
- Acetylsalicylic Acid (ASA) or other NSAIDs, e.g. aspirin, celecoxib, diclofenac, ibuprofen, indomethacin, ketorolac, meloxicam, naproxen. Do NOT take these medicines when you take CAMBIA®.
- Alcohol
- Antidepressants, including Selective Serotonin Reuptake Inhibitors (SSRIs), e.g. citalopram, fluoxetine, paroxetine, sertraline) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs), e.g. duloxetine, desvenlafaxine, venlafaxine)
- Blood pressure medications :
 - ACE (angiotensin converting enzyme inhibitors) e.g. enalapril, lisinopril, perindopril, ramipril
 - ARBs (angiotensin II receptor blockers), e.g. candesartan, irbesartan, losartan, valsartan
- Blood thinners, e.g. warfarin, ASA, clopidogrel
- Corticosteroids (including glucocorticoids), e.g. prednisone
- Cyclosporine
- Digoxin
- Diuretics, e.g. furosemide, hydrochlorothiazide
- Glucocorticoids
- Lithium
- Methotrexate
- Oral contraceptives
- Oral hypoglycemics (diabetes medications)
- Phenytoin
- Probenecid
- Quinolone antibacterials
- Sulfapyrazone
- Tacrolimus

alert. If you become drowsy, dizzy or light-headed after taking CAMBIA®, do NOT drive or operate machinery.

CAMBIA® may cause you to become more sensitive to sunlight. Any exposure to sunlight or sunlamps may cause sunburn, skin blisters, skin rash, redness, itching or discolouration, or vision changes. If you have a reaction from the sun, check with your doctor.

Check with your doctor IMMEDIATELY if you develop chills, fever, muscle aches or pains, or other flu-like symptoms, especially if they occur before or together with a skin rash. These symptoms may be the first signs of a SERIOUS ALLERGIC REACTION to this medication.

SERIOUS SIDE EFFECTS, AND WHAT TO DO ABOUT THEM		
Symptom	STOP taking CAMBIA® and get emergency medical attention IMMEDIATELY	STOP taking CAMBIA® and talk to your doctor or pharmacist
Heart Attack: chest pain, shortness of breath, sweating and anxiety	✓	
Heart failure: shortness of breath especially after exercise, leg/ankle swelling (fluid retention)	✓	
Stroke: face weakness, inability to raise both arms equally and abnormal speech	✓	
Ulcer or bleeding of the stomach or gut: vomit blood or black stools, abdominal pain	✓	
Asthma: shortness of breath, wheezing, any trouble breathing or chest tightness	✓	
Allergic reaction: skin rash, hives, itching or swelling of the face, lips, tongue or throat, difficulty swallowing or breathing	✓	
Vision Changes: blurred vision, or any visual disturbance	✓	

SERIOUS SIDE EFFECTS, AND WHAT TO DO ABOUT THEM		
Symptom	STOP taking CAMBIA® and get emergency medical attention IMMEDIATELY	STOP taking CAMBIA® and talk to your doctor or pharmacist
Jaundice: yellow colour to skin and eyes, with or without itchy skin	✓	
Anemia: low red blood cells		✓
Any pain or difficulty experienced while urinating		✓
Any change in the amount or colour of your urine (red or brown)		✓
Swelling of the feet, lower legs; weight gain		✓
Vomiting that worsens or persistent indigestion, nausea that worsens, stomach pain or diarrhea		✓
Malaise, fatigue, loss of appetite		✓
Headache, stiff neck		✓
Mental confusion, depression		✓
Dizziness, lightheadedness		✓
Hearing problems		✓

This is not a complete list of side effects. For any unexpected effects while taking CAMBIA®, contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature 15-30°C (59-86°F).

Do NOT keep outdated medicine or medicine no longer needed. Any outdated or unused medicine should be returned to your pharmacist.

Keep out of reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

<http://www.aralez.com/> or by contacting the sponsor, Aralez Pharmaceuticals Canada Inc. at: 1-866-391-4503 (toll-free).

This leaflet was prepared by Aralez Pharmaceuticals Canada Inc.

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