CAMBIA - diclofenac potassium powder, for solution
Nautilus Neurosciences, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CAMBIA safely and effectively. See full prescribing information for CAMBIA.
CAMBIA (Diclofenac Potassium for Oral Solution)
Initial U.S. Approval: 1988

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

See full prescribing information for complete boxed warning

Cardiovascular Risk

- **Non-steroidal anti-inflammatory drugs (NSAIDs) may increase the risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. Risk may increase with duration of use. (**5.1**)**
- **CAMBIA is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery. (**4**,** 5.1**)**

Gastrointestinal Risk

- **NSAIDs increase the risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. Events can occur at any time without warning symptoms. Elderly patients are at greater risk. (**5.2**)**

INDICATIONS AND USAGE

CAMBIA is a non-steroidal anti-inflammatory (NSAID) drug indicated for the acute treatment of migraine attacks with or without aura in adults 18 years of age or older (1.1)
Important Limitations (1.2):

- CAMBIA is not indicated for the prophylactic therapy of migraine
- Safety and effectiveness of CAMBIA not established for cluster headache, which is present in an older, predominantly male population

DOSAGE AND ADMINISTRATION

Single 50 mg dose; mix single packet contents with 1 to 2 ounces (30 to 60 mL) of water prior to administration (1)

DOSAGE FORMS AND STRENGTHS

Packets: Each containing buffered diclofenac potassium 50 mg in a soluble powder (3)

CONTRAINDICATIONS

- Known hypersensitivity to diclofenac or NSAIDs (4)
- Pre-existing asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs (4)
- Use during the peri-operative period in the setting of coronary artery bypass graft (CABG) surgery (4, 5.1)

WARNINGS AND PRECAUTIONS

- Serious and potentially fatal CV thrombotic events: Use lowest effective dose of CAMBIA for shortest possible duration (5.1)
- Serious and potentially fatal GI reactions: Use lowest effective dose of CAMBIA for shortest possible duration; use with caution in patients with prior history of ulcer disease or GI bleeding (5.2)
- Hepatic effects: Range from transaminase elevations to liver failure; discontinue CAMBIA immediately if abnormal liver tests persist or worsen (5.3, 5.13)
- Hypertension: Can occur with NSAID treatment. Monitor blood pressure closely during treatment with CAMBIA (5.4)
- Congestive heart failure and edema: Fluid retention and edema can occur with NSAID treatment; use CAMBIA with caution in patients with fluid retention or heart failure (5.5)
- Renal effects: Long-term administration of NSAIDs can result in renal papillary necrosis and other renal injury; use CAMBIA with caution in patients at risk (e.g., the elderly, those with renal impairment, heart failure, liver impairment, and those taking diuretics or ACE inhibitors) (5.6)
- Anaphylactoid reactions: May occur in patients with the aspirin triad or in patients without prior exposure to CAMBIA; discontinue CAMBIA immediately if an anaphylactoid reaction occurs (5.7)
- Serious skin reactions: Include exfoliative dermatitis, Stevens-Johnson Syndrome, and toxic epidermal necrolysis, which can be fatal; discontinue CAMBIA if rash or other signs of local skin reaction occur (5.8)

ADVERSE REACTIONS

Most common adverse reactions (≥1% and >placebo) were nausea and dizziness (6.1)

To report SUSPECTED ADVERSE REACTIONS contact Nautilus Neurosciences, Inc. at 877-874-2440 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Aspirin: Concomitant administration with other NSAIDs, including aspirin, is not recommended because of an increased risk of adverse reactions, including GI bleeding (7.1)
- Anticoagulants: Concomitant use of diclofenac and anticoagulants (e.g., warfarin) increases the risk of serious GI bleeding (7.2)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. Based on human data, starting at 30 weeks gestation, CAMBIA should be avoided as premature closure of the ductus arteriosus in the fetus may occur (5.9, 8.1)
- Nursing Mothers: Use with caution, as it is not known if diclofenac is excreted in human milk (8.3)
- Hepatic insufficiency: The liver metabolizes almost 100% of diclofenac; there is insufficient information available to support dosing recommendations for CAMBIA in patients with hepatic insufficiency (5.3, 8.6, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 4/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

Cardiovascular Risk

Non-steroidal anti-inflammatory drugs (NSAIDs) may increase the risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk [*see Warnings and Precautions (5.1)]*.

CAMBIA is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery [see Contraindications *(4) and Warnings and Precautions (5.1)]*.

Gastrointestinal Risk

NSAIDs increase the risk of serious gastrointestinal (GI) 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 are at greater risk for serious gastrointestinal events [*see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

1.1 Acute Treatment of Migraine

CAMBIA™ (Diclofenac Potassium for Oral Solution) is indicated for the acute treatment of migraine attacks with or without aura in adults (18 years of age or older).

1.2 Important Limitations

- CAMBIA is not indicated for the prophylactic therapy of migraine.
- The safety and effectiveness of CAMBIA have not been established for cluster headache, which is present in an older, predominantly male population.

2 DOSAGE AND ADMINISTRATION

2.1 Acute Treatment of Migraine

Administer one packet (50 mg) of CAMBIA™ for the acute treatment of migraine. Empty the contents of one packet into a cup containing 1 to 2 ounces (30 to 60 mL) of water, mix well and drink immediately. Do not use liquids other than water.

Taking CAMBIA with food may cause a reduction in effectiveness compared to taking CAMBIA on an empty stomach *[see Clinical Pharmacology (12.3)]*.

Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals. The safety and effectiveness of a second dose have not been established.

2.2 Interchangeability With Other Formulations of Diclofenac

Different formulations of oral diclofenac (e.g., CAMBIA, diclofenac sodium enteric-coated tablets, diclofenac sodium extended-release tablets, or diclofenac potassium immediate-release tablets) may not be bioequivalent even if the milligram strength is the same. Therefore, it is not possible to convert dosing from any other formulation of diclofenac to CAMBIA.

3 DOSAGE FORMS AND STRENGTHS

CAMBIA is available in individual packets each designed to deliver a 50 mg dose when mixed in water.

4 CONTRAINDICATIONS

- CAMBIA is contraindicated in patients with known hypersensitivity (e.g., anaphylactoid reactions and serious skin reactions) to diclofenac *[see Warnings and Precautions (5.7, 5.8)]*.
- CAMBIA is contraindicated in patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients *[see Warnings and Precautions (*5.7*, 5.12)]*.
- CAMBIA is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery *[see Warnings and Precautions (*5.1*)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years' duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Inform patients about the signs and symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID increases the risk of serious GI events *[see Warnings and Precautions (5.2)]*.

Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following coronary artery bypass graft (CABG) surgery found an increased incidence of myocardial infarction and stroke *[see Contraindications (4)]*.

5.2 Gastrointestinal Effects - Risk of Ulceration, Bleeding, and Perforation

NSAIDs, including CAMBIA, can cause serious gastrointestinal (GI) adverse events such as inflammation, bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs 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 with longer duration of use, thus increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term NSAID therapy is not without risk.

Prescribe NSAIDs, including CAMBIA, with extreme caution in patients with a prior history of ulcer disease or GI bleeding. Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a greater than 10-fold risk for developing a GI bleed than patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. 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 in patients treated with an NSAID, use the lowest effective dose for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during CAMBIA therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of the CAMBIA until a serious GI adverse event is ruled out. For high risk patients, alternative therapies that do not include NSAIDs should be considered.

5.3 Hepatic Effects

Elevations of one or more liver tests may occur during therapy with CAMBIA. These laboratory abnormalities may progress, may persist, or may only be transient with continued therapy. Borderline elevations (less than 3 times the upper limit of the normal [ULN] range) or greater elevations of transaminases occurred in about 15% of diclofenac-treated patients. Of the markers of hepatic function, ALT (SGPT) is recommended for the monitoring of liver injury.

In clinical trials, meaningful elevations (i.e., more than 3 times the ULN) of AST (SGOT) 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, 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 times the ULN) in about 1% of the 3,700 patients. In this open-label study, a higher incidence of borderline (less than 3 times the ULN), moderate (3–8 times the ULN), and marked (>8 times the ULN) elevations of ALT or AST was observed in patients receiving diclofenac when compared to other NSAIDs.. Almost all meaningful elevations in transaminases were detected before patients became symptomatic.

Abnormal tests occurred during the first 2 months of therapy with diclofenac in 42 of the 51 patients in all trials who developed marked transaminase elevations. In postmarketing reports, cases of drug-induced hepatotoxicity have been reported in the first month, and in some cases, the first 2 months of NSAID therapy, but can occur at any time during treatment with diclofenac.

Postmarketing 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.

Measure transaminases (ALT and AST) periodically in patients receiving long-term therapy with diclofenac because severe hepatotoxicity may develop without a prodrome of distinguishing symptoms. The optimum times for making the first and subsequent transaminase measurements are not known. Based on clinical trial data and postmarketing experiences, transaminases should be monitored within 4 to 8 weeks after initiating treatment with diclofenac. However, severe hepatic reactions can occur at any time during treatment with diclofenac. If abnormal liver tests persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, abdominal pain, diarrhea, dark urine, etc.), discontinue CAMBIA immediately.

To minimize the possibility that hepatic injury will become severe between transaminase measurements, inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms), and the appropriate action patients should take if these signs and symptoms appear.

To minimize the potential risk for an adverse liver-related event in patients treated with CAMBIA, use the lowest effective dose for the shortest duration possible. Exercise caution when prescribing CAMBIA with concomitant drugs that are known to be potentially hepatotoxic (e.g., acetaminophen, certain antibiotics, antiepileptics). Caution patients to avoid taking nonprescription acetaminophen-containing products while using CAMBIA.

5.4 Hypertension

NSAIDs, including CAMBIA, can lead to new onset or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Use NSAIDs, including CAMBIA, with caution in patients with hypertension. Monitor blood pressure closely during the initiation of NSAID treatment and throughout the course of therapy.

Patients taking ACE inhibitors, thiazides, or loop diuretics may have impaired response to these therapies when taking NSAIDs.

5.5 Congestive Heart Failure and Edema

Fluid retention and edema have been observed in some patients taking NSAIDs. Use CAMBIA with caution in patients with fluid retention or heart failure.

5.6 Renal Effects

Use caution when initiating treatment with CAMBIA in patients with considerable dehydration.

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics or ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

No information is available from controlled clinical studies regarding the use of CAMBIA in patients with advanced renal disease. Therefore, treatment with CAMBIA is not recommended in patients with advanced renal disease. If CAMBIA therapy must be initiated, close monitoring of the patient's renal function is advisable.

5.7 Anaphylactoid Reactions

As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to CAMBIA. CAMBIA is contraindicated in patients with the aspirin 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 aspirin or other NSAIDs. *[see Contraindications (4)]*.

5.8 Serious Skin Reactions

NSAIDs, including CAMBIA, can cause serious skin adverse reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin manifestations and to discontinue CAMBIA at the first appearance of skin rash or any other sign of hypersensitivity.

5.9 Pregnancy

CAMBIA can cause fetal harm when administered to a pregnant woman. Starting at 30 weeks gestation, CAMBIA and other NSAIDs should be avoided by pregnant women as premature closure of the ductus arteriosus in the fetus may occur. If this drug is used during this time period in pregnancy, the patient should be apprised of the potential hazard to a fetus *[see Use in Special Populations (*8.1*)]*.

5.10 Masking of Inflammation and Fever

The pharmacological activity of NSAIDs in reducing inflammation and possibly fever may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions.

5.11 Hematologic Effects

Anemia may occur in patients receiving NSAIDs. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis. In patients on long-term therapy with NSAIDs, including CAMBIA, check hemoglobin or hematocrit if they exhibit any signs or symptoms of anemia or blood loss.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, the NSAID effect on platelet function is quantitatively less, of shorter duration, and reversible. Carefully monitor patients treated with CAMBIA who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants.

5.12 Use in Patients With Pre-existing Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross-reactivity, including bronchospasm, between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, CAMBIA is contraindicated in patients with this form of aspirin sensitivity and should be used with caution in all patients with pre-existing asthma.

5.13 Monitoring

Because serious GI ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding.

For patients on long-term treatment with NSAIDs, including CAMBIA, periodically perform a CBC and chemistry profile. Discontinue CAMBIA if abnormal liver tests or renal tests persist or worsen.

5.14 Phenylketonurics

CAMBIA contains aspartame equivalent to phenylalanine 25 mg per packet.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Cardiovascular thrombotic events *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Gastrointestinal effects *[see Boxed Warning and Warnings and Precautions (5.2)]*
- Hepatic effects *[see Warnings and Precautions (5.3)]*
- Hypertension *[see Warnings and Precautions (5.4)]*
- Congestive Heart Failure and Edema *[see Warnings and Precautions (5.5)]*
- Renal Effects *[see Warnings and Precautions (5.6)]*
- Anaphylactoid Reactions *[see Warnings and Precautions (5.7)]*
- Serious Skin Reactions *[see Warnings and Precautions (5.8)]*

The most common adverse reactions reported with CAMBIA are nausea and dizziness.

The most common adverse events resulting in discontinuation of patients following CAMBIA dosing in controlled clinical trials were urticaria (0.2%) and flushing (0.2%).

6.1 Clinical Studies Experience With CAMBIA

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of a single dose of CAMBIA was evaluated in 2 placebo-controlled trials with a total of 634 migraine patients treated with CAMBIA for a single migraine headache. Following treatment with

diclofenac potassium (either CAMBIA or diclofenac potassium immediate-release tablets [as a control]), 5 subjects (0.8%) withdrew from the studies; following placebo exposure, 1 subject (0.2%) withdrew. No withdrawals were due to a serious reaction.

The most common adverse reactions (i.e., that occurred in 1% or more of CAMBIA-treated patients) and more frequent with CAMBIA than with placebo were nausea and dizziness (see Table 1).

Table 1: Treatment-Related Adverse Reactions With Incidence >1% and Greater Than Placebo in Studies 1 and 2 Combined

Disorder Event	**CAMBIA** N=634	**Placebo** N=646
Gastrointestinal		
Nausea	3%	2%
Nervous System		
Dizziness	1%	0.5%

6.2 Adverse Reactions Reported With Diclofenac and Other NSAIDs

In patients taking diclofenac or other NSAIDs, the most frequently reported adverse reactions occurring in approximately 1%-10% of patients are:

GI reactions (including abdominal pain, constipation, diarrhea, dyspepsia, flatulence, gross bleeding/perforation, heartburn, nausea, GI ulcers [gastric/duodenal], and vomiting), abnormal renal function, anemia, dizziness, edema, elevated liver enzymes, headaches, increased bleeding time, pruritus, rashes, and tinnitus.

Additional adverse reactions reported in patients taking NSAIDs include occasionally:

Body as a Whole: Fever, infection, sepsis

Cardiovascular System: Congestive heart failure, hypertension, tachycardia, syncope

Digestive System: Dry mouth, esophagitis, gastric/peptic ulcers, gastritis, gastrointestinal bleeding, glossitis, hematemesis, hepatitis, jaundice

Hemic and Lymphatic System: Ecchymosis, eosinophilia, leukopenia, melena, purpura, rectal bleeding, stomatitis, thrombocytopenia

Metabolic and Nutritional: Weight changes

Nervous System: Anxiety, asthenia, confusion, depression, dream abnormalities, drowsiness, insomnia, malaise, nervousness, paresthesia, somnolence, tremors, vertigo

Respiratory System: Asthma, dyspnea

Skin and Appendages: Alopecia, photosensitivity, sweating increased

Special Senses: Blurred vision

Urogenital System: Cystitis, dysuria, hematuria, interstitial nephritis, oliguria/polyuria, proteinuria, renal failure

Other adverse reactions in patients taking NSAIDs, which occur rarely , are:

Body as a Whole: Anaphylactic reactions, appetite changes, death

Cardiovascular System: Arrhythmia, hypotension, myocardial infarction, palpitations, vasculitis

Digestive System: Colitis, eructation, liver failure, pancreatitis

Hemic and Lymphatic System: Agranulocytosis, hemolytic anemia, aplastic anemia, lymphadenopathy, pancytopenia

Metabolic and Nutritional: Hyperglycemia

Nervous System: Convulsions, coma, hallucinations, meningitis

Respiratory System: Respiratory depression, pneumonia

Skin and Appendages: Angioedema, toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, urticaria

Special Senses: Conjunctivitis, hearing impairment

7 DRUG INTERACTIONS

7.1 Aspirin

When administered with aspirin, diclofenac potassium's protein binding is reduced. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of CAMBIA and aspirin is not generally recommended because of the potential of increased adverse effects.

7.2 Anticoagulants

The effects of anticoagulants such as warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than that with use of either drug alone.

7.3 ACE Inhibitors

NSAIDs may diminish the antihypertensive effect of ACE inhibitors. This interaction should be given consideration in patients taking CAMBIA concomitantly with ACE inhibitors.

7.4 Diuretics

Clinical studies, as well as post-marketing observations, have shown that diclofenac potassium can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, observe patients closely for signs of renal failure as well as to assure diuretic efficacy *[see Warnings and Precautions (*5.6*)]*.

7.5 Lithium

NSAIDs have produced elevations of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. 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.

7.6 Methotrexate

NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This indicates that NSAIDs may enhance the toxicity of methotrexate. Use caution when NSAIDs are administered concomitantly with methotrexate.

7.7 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.

7.8 Inhibitors of Cytochrome P450 2C9

Diclofenac is metabolized predominantly by Cytochrome P-450 CYP2C9. Co-administration of medications that inhibit CYP2C9 may affect the pharmacokinetics of diclofenac *[see Clinical Pharmacology (*12.3*)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C prior to 30 weeks gestation; Category D starting at 30 weeks gestation.

Starting at 30 weeks gestation, CAMBIA, and other NSAIDS, should be avoided by pregnant women as premature closure of the ductus arteriosus in the fetus may occur *[see Warnings and Precautions (5.9)]*. There are no adequate and well controlled studies in pregnant women.

Prior to 30 weeks gestation, CAMBIA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Reproductive studies have been performed in mice given diclofenac sodium (up to 20 mg/kg/day, 2 times the recommended human dose [RHD] of 50 mg/day on a body surface area [mg/m^2 basis), and in rats and rabbits given diclofenac sodium (up to 10 mg/kg/day; 2 [rats] and 4 [rabbits] times the RHD on a mg/m^2 basis) and have revealed no evidence of teratogenicity despite the induction of maternal toxicity and fetal toxicity. In rats, maternally toxic doses were associated with dystocia, prolonged gestation, reduced fetal weights and growth, and reduced fetal survival.

8.2 Labor and Delivery

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.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from CAMBIA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of CAMBIA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Elderly patients are at increased risk for serious GI adverse events.

Diclofenac is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken when using CAMBIA in the elderly.

8.6 Hepatic Impairment

Because hepatic metabolism accounts for almost 100% of diclofenac elimination, patients with

hepatic impairment should be considered for treatment with CAMBIA only if the benefits outweigh the risks. There is insufficient information available to support dosing recommendations for CAMBIA in patients with hepatic insufficiency. *[see Clinical Pharmacology (*12.3*)]*.

8.7 Renal Impairment

No information is available from controlled clinical studies regarding the use of CAMBIA in patients with advanced renal disease. Therefore, treatment with CAMBIA is not recommended in patients with advanced renal disease. If CAMBIA therapy must be initiated, close monitoring of the patient's renal function is advisable.

10 OVERDOSAGE

Symptoms following acute NSAID overdoses are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, 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.

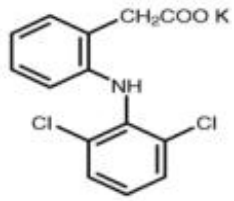
Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose (5 to 10 times the usual dose). Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

11 DESCRIPTION

CAMBIA (Diclofenac Potassium for Oral Solution) is a benzeneacetic acid derivative NSAID. CAMBIA is available as a buffered soluble powder, designed to be mixed with water prior to oral administration.

CAMBIA is a white to off-white, buffered, flavored powder for oral solution packaged in individual unit dose packets *[see How Supplied/Storage and Handling (16)]*.

The chemical name for diclofenac potassium is 2-[(2,6-dichlorophenyl)amino] benzeneacetic acid monopotassium salt. The molecular weight of diclofenac potassium is 334.25. Its molecular formula is $C_{14}H_{10}Cl_2NKO_2$, and it has the following structural formula:



The inactive ingredients in CAMBIA include: aspartame (equivalent to 25 mg phenylalanine), flavoring agents (anise and mint), glycerol behenate, mannitol, potassium bicarbonate, and saccharin sodium.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CAMBIA is a non-steroidal anti-inflammatory drug (NSAID). The mechanism of action of CAMBIA, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition.

12.3 Pharmacokinetics

Absorption: Diclofenac is 100% absorbed after oral administration compared to intravenous administration as measured by urine recovery. However, due to first-pass metabolism, only about 50% of the absorbed dose is systemically available. In fasting volunteers, measurable plasma levels were observed within 5 minutes of dosing with CAMBIA. Peak plasma levels were achieved at approximately 0.25 hour in fasting normal volunteers, with a range of 0.17 to 0.67 hours. High fat food had no significant effect on the extent of diclofenac absorption, but there was a reduction in peak plasma levels of approximately 70% after a high fat meal. Decreased Cmax may be associated to decreased effectiveness.

Distribution: The apparent volume of distribution (V/F) of diclofenac potassium is 1.3 L/kg.

Diclofenac is more than 99% bound to human serum proteins, primarily to albumin. Serum protein binding is constant over the concentration range (0.15-105 µg/mL) achieved with recommended doses.

Metabolism: Five diclofenac metabolites have been identified in human plasma and urine. The metabolites include 4'-hydroxy-, 5-hydroxy-, 3'-hydroxy-, 4',5-dihydroxy- and 3'-hydroxy-4'-methoxy diclofenac. The major diclofenac metabolite, 4'-hydroxydiclofenac, 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. Acylglucuronidation 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- hydroxydiclofenac were approximately 50% and 4% of the parent compound after single oral dosing compared to 27% and 1% in normal healthy subjects.

Excretion: Diclofenac is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites. Little or no free unchanged diclofenac is excreted in the urine. Approximately 65% of the dose is excreted in the urine and approximately 35% in the bile as conjugates of unchanged diclofenac plus metabolites. Because renal elimination is not a significant pathway of elimination for unchanged diclofenac, dosing adjustment in patients with mild to moderate renal dysfunction is not necessary. The terminal half-life of unchanged diclofenac is approximately 2 hours.

Special Populations:

Race: There are no pharmacokinetic differences due to race.

Hepatic Impairment: The liver metabolizes almost 100% of diclofenac; there is insufficient information available to support dosing recommendations for CAMBIA in patients with hepatic insufficiency (5.3, 8.6)

Renal Impairment: In patients with renal impairment (inulin clearance 60-90, 30-60, and <30 mL/min; N=6 in each group), AUC values and elimination rate were comparable to those in healthy subjects.

13 NON-CLINICAL STUDIES

13.1 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 m/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 tk) 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.

14 CLINICAL STUDIES

The efficacy of CAMBIA in the acute treatment of migraine headache was demonstrated in two randomized, double-blind, placebo-controlled trials.

Patients enrolled in these two trials were predominantly female (85%) and white (86%), with a mean age of 40 years (range: 18 to 65). Patients were instructed to treat a migraine of moderate to severe pain with 1 dose of study medication. Patients evaluated their headache pain 2 hours later. Associated symptoms of nausea, photophobia, and phonophobia were also evaluated. In addition, the proportion of patients who were “sustained pain free”, defined as a reduction in headache severity from moderate or severe pain to no pain at 2 hours post-dose without a return of mild, moderate, or severe pain and no use of rescue medication for 24 hours post-dose, was also evaluated. In these studies, the percentage of patients achieving pain freedom 2 hours after treatment and sustained pain freedom from 2 to 24 hours post-dose was significantly greater in patients who received CAMBIA compared with those who received placebo (see Table 2). The percentage of patients achieving pain relief 2 hours after treatment (defined as a reduction in headache severity from moderate or severe pain to mild or no pain) was also significantly greater in patients who received CAMBIA compared with those who received placebo (see Table 2).

Table 2: Percentage of Patients With 2-Hour Pain Freedom, Sustained Pain Freedom 2-24 Hours, and 2-Hour Pain Relief Following Treatment

Study 1	**CAMBIA (n=265)**	**Placebo (n=257)**
2-Hour Pain Free	24%	13%
2-24h Sustained Pain Free	22%	10%
2-Hour Pain Relief	48%	27%
Study 2	**CAMBIA (n=343)**	**Placebo (n=347)**
2-Hour Pain Free	25%	10%
2-24h Sustained Pain Free	19%	7%
2-Hour Pain Relief	65%	41%

The estimated probability of achieving migraine headache pain freedom within 2 hours following treatment with CAMBIA is shown in Figure 1.

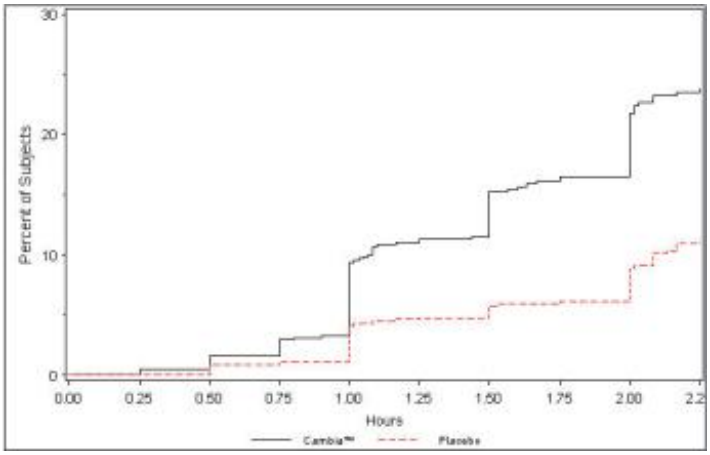


Figure 1. Percentage of Patients With Initial Headache Pain Freedom Within 2 Hours

There was a decreased incidence of nausea, photophobia and phonophobia following administration of CAMBIA, compared to placebo. The efficacy and safety of CAMBIA was unaffected by age or gender of the patient.

16 HOW SUPPLIED/STORAGE AND HANDLING

CAMBIA™ 50 mg (Diclofenac Potassium for Oral Solution) is supplied as one or more sets of three perforated co-joined individual dose packets. Each individual packet 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 unit dose packets.

Individual CAMBIA™ Packets - NDC 50192-113-01

Boxes of nine (9) CAMBIA™ Packets - NDC 50192-113-09

Store at 25°C (77°F) Excursions permitted from 15°C-30°C (59°F-86°F). [See USP Controlled Room Temperature]

Manufactured by:
MIPHARM S.p.A.
Via Bernardo Quaranta, 12
20141 Milan, Italy

Manufactured for:
Nautilus Neurosciences, Inc.
135 Rte. 202/206
Bedminster, NJ 08921
United States of America

Manufactured and Distributed Under License from APR Applied Pharma Research SA, Balerna Switzerland

17 PATIENT COUNSELING INFORMATION

Inform patients of the availability of a Medication Guide for NSAIDs that accompanies each prescription dispensed, and instruct them to read the Medication Guide prior to using CAMBIA *[see Medication Guide (17.9)]*.

17.1 Cardiovascular Effects

CAMBIA, like other NSAIDS, may cause serious CV events, such as MI or stroke, which may result in hospitalization and even death. Although serious CV events can occur without warning symptoms, advise patients to be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and to ask for medical advice when observing any indicative sign or symptoms. Inform patients of the importance of this follow-up *[see Warnings and Precautions (5.1)]*.

17.2 Gastrointestinal Effects

CAMBIA, like other NSAIDS, can cause GI discomfort and more serious GI adverse events such as ulcers and bleeding, which may result in hospitalization and even death. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, advise patients to be alert for the signs and symptoms of ulcerations and bleeding, and to ask for medical advice when observing any indicative sign or symptoms including epigastric pain, dyspepsia, melena, and hematemesis. Inform patients of the importance of this follow-up *[see Warnings and Precautions (5.2)]*.

17.3 Hepatotoxicity

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and “flulike” symptoms). Instruct patients to stop therapy with CAMBIA and seek immediate medical therapy if any of these occur *[see Warnings and Precautions (*5.3*)]*.

17.4 Weight Gain and Edema

Advise patients to promptly report to their physicians signs or symptoms of unexplained weight gain or edema during treatment with CAMBIA *[see Warnings and Precautions (*5.5*)]*.

17.5 Anaphylactoid Reactions

Inform patients of the signs of an anaphylactoid reaction (e.g., difficulty breathing, swelling of the face or throat). Instruct patients to seek immediate emergency help if these occur *[see Warnings and Precautions (5.7)]*.

17.6 Adverse Skin Reactions

CAMBIA, like other NSAIDS, can cause serious skin reactions such as exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrosis (TEN), which may result in hospitalizations and even death. Although serious skin reactions may occur without warning, advise patients to be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and to ask for medical advice when observing any indicative signs or symptoms. Advise patients to stop CAMBIA immediately if they develop any type of rash and to contact their physicians as soon as possible *[see Warnings and Precautions (5.8)]*.

17.7 Effects During Pregnancy

Starting at 30 weeks gestation, CAMBIA and other NSAIDs should be avoided by pregnant women as premature closure of the ductus arteriosus in the fetus may occur *[see Use in Specific Populations (8.1)]*.

17.8 Phenylketonurics

CAMBIA packets contain aspartame equivalent to phenylalanine 25 mg per packet.

17.9 FDA-Approved Medication Guide

Upon dispensing to a patient please ensure the patient receives the attached Medication Guide.

MEDGUIDE

MEDICATION GUIDE

CAMBIA (Cam-bē- or Cam-bē-a)
(diclofenac potassium for oral solution)

Read the Patient Information that comes with CAMBIA before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about CAMBIA?

CAMBIA, which contains diclofenac, (a non-steroidal anti-inflammatory drug or NSAID), may increase your chance of a heart attack or stroke that can lead to death. This chance is higher:

- with longer use of NSAID medicines
- in people who have heart disease

NSAID medicines, such as CAMBIA, should never be used right before or after a heart surgery called a "coronary artery bypass graft" (CABG).

NSAID medicines, such as CAMBIA, can cause ulcers and bleeding in your stomach and intestines at any time during treatment.

Ulcers and bleeding:

- can happen without warning symptoms
- may cause death

The chance of a person getting an ulcer or bleeding increases with:

- the use of medicines called steroid hormones (corticosteroids) and blood thinners (anticoagulants)
- longer or regular use
- smoking
- drinking alcohol
- older age
- having poor health

CAMBIA should only be used:

- exactly as prescribed
- at the lowest dose possible for your treatment
- for the shortest time needed

What is CAMBIA?

CAMBIA is a prescription medicine used to treat migraine attacks in adults. It does not prevent or lessen the number of migraines you have, and it is not for other types of headaches. CAMBIA contains diclofenac potassium (a Non-Steroidal Anti-Inflammatory Drug or NSAID).

How should I take CAMBIA?

Take CAMBIA exactly as your healthcare provider tells you to take it.

Take 1 dose of CAMBIA to treat your migraine headache:

- remove one single dose packet from a set of three packets
- open packet only when you are ready to use it
- empty contents of packet into 1 to 2 ounces (2 to 4 tablespoons) of water
- mix well and drink the water and powder mixture
- throw away empty packet in a safe place and out of the reach of children
- taking CAMBIA with food may cause a reduction in effectiveness compared to taking CAMBIA on an empty stomach
- do not take more CAMBIA than directed by your healthcare provider. In case of overdose, get

medical help or contact a Poison Control Center right away

Who should not take CAMBIA?

Do not take CAMBIA:

- right before or after heart bypass surgery. See "What is the most important information I should know about CAMBIA?"
- if you have or have had an asthma attack, hives, or other allergic reaction with aspirin, diclofenac, or any other NSAID medicine

Before you take CAMBIA, tell your healthcare provider about all your medical conditions, including if you:

- have a history of stomach ulcer or bleeding in your stomach or intestines
- have kidney or liver problems
- have any allergies to any medicines
- have chest pain, shortness of breath, irregular heartbeats
- are pregnant, think you might be pregnant, or are trying to become pregnant. CAMBIA should not be used by pregnant women, especially during the last 3 months of pregnancy unless directed by your healthcare provider to do so. CAMBIA may cause problems in your unborn child or complications during your delivery
- are breastfeeding or plan to breastfeed. It is not known if CAMBIA passes into your breast milk. You and your doctor should decide if you will take CAMBIA or breastfeed. You should not do both
- have a headache that is different from your usual migraine

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

CAMBIA and other medicines may affect each other, causing side effects. CAMBIA may affect the way other medicines work, and other medicines may affect how CAMBIA works.

Especially tell your doctor if you take:

- aspirin
- any anticoagulant medicines (warfarin, Coumadin, Jantoven)

Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist when you get a new medicine.

What are the possible side effects of CAMBIA?

Serious side effects include:

- heart attack
- stroke
- high blood pressure
- heart failure from body swelling (fluid retention)
- kidney problems including kidney failure
- bleeding and ulcers in the stomach and intestine
- low red blood cells (anemia)
- life-threatening skin reactions
- life-threatening allergic reactions
- liver problems including life-threatening liver failure
- asthma attacks in people who have asthma

Get emergency help right away if you have any of the following symptoms of heart attack or stroke:

- shortness of breath or trouble breathing

- chest pain
- swelling of your face or throat
- weakness in one part or one side of your body
- slurred speech

Common side effects include:
- nausea
- dizziness

Stop CAMBIA and call your healthcare provider right away if you have any of the following symptoms:
- nausea that seems out of proportion to your migraine
- stomach pain
- sudden or severe pain in your belly
- vomit blood
- blood in your bowel movement or it is black and sticky like tar
- itching
- skin rash or blisters with fever
- yellow skin or eyes
- swelling of your arms and legs, hands and feet
- unusual weight gain
- more tired or weaker than usual
- flu-like symptoms

Tell your healthcare provider if you have any side effects that bother you or do not go away.

These are not all the side effects with NSAID medicines. Talk to your healthcare provider or pharmacist for more information about NSAID medicines.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store CAMBIA?
- store CAMBIA in a dry place at room temperature between 59° to 86°F (15° to 30°C)
- keep CAMBIA and all medicines out of reach of children

General information about CAMBIA
- medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use CAMBIA for a condition for which it was not prescribed
- do not give CAMBIA to other people, even if they have the same problem you have. It may harm them
- this Medication Guide contains the most important information about CAMBIA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider for information written for healthcare professionals
- for more information call Nautilus Neurosciences, Inc at 877-874-2440 (weekdays 9 AM to 5 PM EST) or through our website at www.nautilusneurosciences.com

What are the ingredients in CAMBIA?

Active ingredients: diclofenac potassium

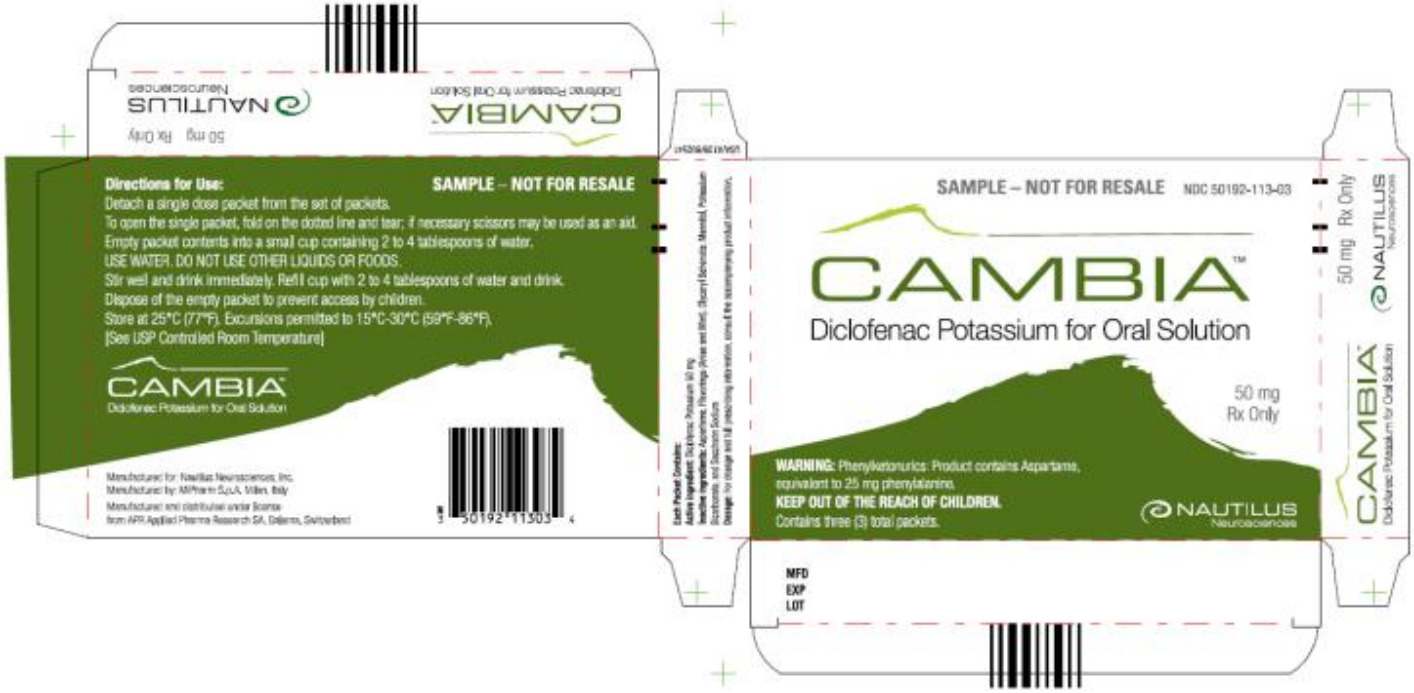
Inactive ingredients: aspartame (equivalent to 25 mg phenylalanine), flavoring agents (anise and mint), glyceryl behenate, mannitol, potassium bicarbonate, and saccharin sodium

Rx only
Issued June 2009
Nautilus Neurosciences, Inc.
Bedminster, NJ 07921
United States of America

This Medication Guide has been approved by the U.S. Food and Drug Administration.

PRINCIPAL DISPLAY PANEL

CAMBIA™
Diclofenac Potassium for Oral Solution
50 mg
Rx Only
WARNING: Phenylketonurics: Product contains Aspartame, equivalent to 25 mg phenylalanine
KEEP OUT OF THE REACH OF CHILDREN.
Contains three (3) total packets.
NAUTILUS
NEROSCIENCES



CAMBIA

diclofenac potassium powder, for solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:50192-113
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
DICLOFENAC POTASSIUM (UNII: L4D5UA6CB4) (DICLOFENAC - UNII:144O8QL0L1)	DICLOFENAC POTASSIUM	1 mg in 1 mg

Inactive Ingredients

Ingredient Name	Strength
ASPARTAME (UNII: Z0H242BBR1)	
GLYCERYL BEHENATE (UNII: R8WTH25YS2)	
MANNITOL (UNII: 3OWL53L36A)	
POTASSIUM BICARBONATE (UNII: HM5Z15LEBN)	
SACCHARIN SODIUM (UNII: SB8ZUX40TY)	

Product Characteristics

Color		**Score**	
Shape		**Size**	
Flavor	ANISE, MINT	**Imprint Code**	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:50192-113-09	09 in 1 BOX		
1		50 mg in 1 PACKET		
2	NDC:50192-113-01	50 mg in 1 PACKET		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA022165	04/20/2010	

Labeler - Nautilus Neurosciences, Inc. (832800770)

Establishment

Name	Address	ID/FEI	Business Operations
MIPHARM SPA		514042399	MANUFACTURE

Revised: 3/2012 Nautilus Neurosciences, Inc.