PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]FLOCTAFENINE

Floctafenine Tablets

Tablets, 200 mg and 400 mg, Oral

Nonsteroidal Anti-Inflammatory Agent

AA PHARMA INC.

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RECENT MAJOR LABEL CHANGES

2 CONTRAINDICATIONS	04/2024
3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Risk of Cardiovascular (CV) Adverse Events	04/2024
3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Risk of Gastrointestinal (GI) Adverse Events	04/2024
3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Risk in Pregnancy	04/2024
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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

FLOCTAFENINE (floctafenine tablets) is indicated for:

- short-term use in acute pain of mild and moderate severity.

For patients with an increased risk of developing CV and/or GI adverse events, other management strategies that do NOT include the use of NSAIDs should be considered first (see 2 CONTRAINDICATIONS and Cardiovascular, and Gastrointestinal)**.**

Use of FLOCTAFENINE should be limited to the lowest effective dose for the shortest possible duration of treatment in order to minimize the potential risk for cardiovascular or gastrointestinal adverse events (see 2 CONTRAINDICATIONS and Cardiovascular, and Gastrointestinal).

FLOCTAFENINE, as a NSAID, does NOT treat clinical disease or prevent its progression.

FLOCTAFENINE, as a NSAID, only relieves symptoms and decreases inflammation for as long as the patient continues to take it.

1.1 Pediatrics

Pediatrics (<18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of FLOCTAFENINE in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use (see 2 CONTRAINDICATIONS and 7.1.3 Pediatrics).

1.2 Geriatrics

Geriatrics (>65years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness (see 4.2 Recommended Dose and Dosage Adjustment, 7 WARNINGS AND PRECAUTIONS, General and 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

FLOCTAFENINE (floctafenine tablets) is contraindicated in:

- Known or suspected hypersensitivity to the drug or other non-steroidal anti-inflammatory drugs or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- The peri-operative setting of coronary artery bypass graft surgery (CABG). Although FLOCTAFENINE 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 (see 7.1.1 Pregnant Women).
- Women who are breastfeeding, because of the potential for serious adverse reactions in nursing infants (see 7.1.2 Breast-feeding).
- Severe uncontrolled heart failure (see Cardiovascular).
- 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. 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 7 WARNINGS AND PRECAUTIONS, Immune, Anaphylactoid Reactions).

  On occasion, it has been observed that intermittent use may have resulted in increased sensitivity. Since severe cases of hypersensitivity reactions have been reported with floctafenine, its use in severe cardiac insufficiency and ischemic cardiomyopathy is contraindicated.
- Active gastric / duodenal / peptic ulcer, active GI bleeding (see Gastrointestinal).
- Cerebrovascular bleeding or other bleeding disorders.
- Inflammatory bowel disease.
- Severe liver impairment or active liver disease (see Hepatic/Biliary/Pancreatic).
- 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 7 WARNINGS AND PRECAUTIONS, Renal).
- Known hyperkalemia (see 7 WARNINGS AND PRECAUTIONS, Renal, Fluid and Electrolyte Balance).
- Children and adolescents less than 18 years of age.
- FLOCTAFENINE is not recommended for use with other NSAIDs because of the absence of any evidence demonstrating synergistic benefits and the potential for additive side effects (see 9.1 Serious Drug Interactions).
- Coronary heart disease.
- Associated treatment with beta-blocking agents (see 9.1 Serious Drug Interactions).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Risk of Cardiovascular (CV) Adverse Events (see 7 WARNINGS AND PRECAUTIONS - Cardiovascular):

  FLOCTAFENINE is a non-steroidal anti-inflammatory drug (NSAID). Use of some NSAIDs is associated with an increased incidence of cardiovascular adverse events (such as myocardial infarction, stroke or thrombotic events) which can be fatal. The risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

  Caution should be exercised in prescribing FLOCTAFENINE to any patient with ischemic heart disease (including but NOT limited to acute myocardial infarction, history of myocardial infarction and/or angina), cerebrovascular disease (including but NOT limited to stroke, cerebrovascular accident, transient ischemic attacks and/or amaurosis fugax) and/or congestive heart failure (NYHA II-IV).

  Use of NSAIDs, such as FLOCTAFENINE, 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 7 WARNINGS AND PRECAUTIONS, Renal, Fluid and Electrolyte Balance).

  Randomized clinical trials with FLOCTAFENINE have not been designed to detect differences in cardiovascular events in a chronic setting. Therefore, caution should be exercised when prescribing FLOCTAFENINE.

- **Risk of Gastrointestinal (GI) Adverse Events** (see 7 WARNINGS AND PRECAUTIONS – Gastrointestinal):

  Use of NSAIDs, such as FLOCTAFENINE, is associated with an increased incidence of gastrointestinal adverse events (such as peptic/duodenal ulceration, perforation, obstruction and gastrointestinal bleeding).

- **Risk in Pregnancy:** Caution should be exercised in prescribing FLOCTAFENINE during the first and second trimesters of pregnancy. Use of NSAIDS at approximately 20 weeks of gestation or later may cause fetal renal dysfunction leading to oligohydramnios and neonatal renal impairment or failure (see 7.1.1 Pregnant Women). FLOCTAFENINE is contraindicated for use during the third trimester because of risk of premature closure of the ductus arteriosus and uterine inertia (prolonged parturition) (see 2 CONTRAINDICATIONS).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Use of FLOCTAFENINE should be limited to the lowest effective dose for the shortest possible duration of treatment in order to minimize the potential risk for cardiovascular or gastrointestinal adverse events (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS).

4.2 Recommended Dose and Dosage Adjustment

Adults: The usual adult dose of FLOCTAFENINE (floctafenine) is 200 to 400 mg every 6 to 8 hours as required. The maximum recommended daily dose is 1200 mg. FLOCTAFENINE is recommended for short-term management of acute pain.

Pediatrics: FLOCTAFENINE is not recommended for use in children (see 2 CONTRAINDICATIONS and 7.1.3 Pediatrics).

Geriatrics: Elderly and debilitated individuals are most susceptible to adverse events from non-steroidal anti-inflammatory drugs, the incidence of which increases with dose and duration of treatment. For such patients, consideration should be given to a starting dose lower than usual, with individual adjustment when necessary and under close supervision (see 7.1.4 Geriatrics).

Adults with renal insufficiency: serum levels are slightly elevated and the dose may therefore be reduced (see 7 WARNINGS AND PRECAUTIONS, Renal).

4.4 Administration

The tablets should be taken after a meal or food with a glass of water.

4.5 Missed Dose

If the patient misses a dose, instruct the patient to take the dose as soon as they remember. If it is almost time for the next dose, inform the patient to skip the missed dose and continue the regular dosing schedule.

5 OVERDOSAGE

A few cases of overdose have been reported with floctafenine. No common symptoms resulting from overdosing could be distinguished among these patients. In all cases the outcome was favourable and the patients recovered well. Standard procedures to evacuate gastric contents, maintain urinary output and provide general supportive care should be employed in cases of overdose.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet 200 mg, 400 mg of floctafenine	Colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose and stearic acid.

FLOCTAFENINE 200 mg: each creamy white, round, biconvex tablet engraved "FLO" over "200" on one side other side plain, contains 200 mg floctafenine. Available in bottle of 100 tablets.

FLOCTAFENINE 400 mg: each creamy white, round, biconvex tablet engraved "FLO" over "400" on one side other side plain, contains 400 mg floctafenine. Available in bottle of 100 tablets.

FLOCTAFENINE is a Schedule F (prescription) drug.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

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.

FLOCTAFENINE 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 9.4 Drug-Drug Interactions, Acetylsalicylic acid (ASA) or other NSAIDs).

Carcinogenesis and Mutagenesis

See 16 NON-CLINICAL TOXICOLOGY, Carcinogenicity.

Cardiovascular

FLOCTAFENINE is a non-steroidal anti-inflammatory drug (NSAID). Use of some NSAIDs is associated with an increased incidence of cardiovascular adverse events (such as myocardial infarction, stroke or thrombotic events) which can be fatal. The risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

Caution should be exercised in prescribing FLOCTAFENINE to patients with risk factors for

cardiovascular disease, cerebrovascular disease or renal disease, such as any of the following (NOT an exhaustive list):

- 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 FLOCTAFENINE, 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 FLOCTAFENINE should hypertension either develop or worsen with its use.

Use of NSAIDs, such as FLOCTAFENINE, can induce fluid retention and edema, and may exacerbate congestive heart failure, through a renally-mediated mechanism (see 7 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.

Since severe cases of hypersensitivity reactions have been reported with floctafenine, its use in severe cardiac insufficiency and ischemic cardiomyopathy is contraindicated.

Endocrine and Metabolism

Corticosteroids: FLOCTAFENINE (floctafenine) 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 9.4 Drug-Drug Interactions, Glucocorticoids).

Gastrointestinal

Serious GI toxicity (sometimes fatal), such as peptic / duodenal ulceration, inflammation, perforation, obstruction and gastrointestinal bleeding, sometimes severe and occasionally fatal can occur at any time, with or without warning symptoms, in patients treated with non-steroidal anti-inflammatory drugs (NSAIDs) including FLOCTAFENINE.

Minor upper GI problems, such as dyspepsia, are common, usually developing early in therapy. Healthcare professionals should remain alert for ulceration and bleeding in patients treated with FLOCTAFENINE, 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 7.1.4 Geriatrics).

Patients should be informed about the signs and/or symptoms of serious GI toxicity and instructed to discontinue using FLOCTAFENINE 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. In patients observed in clinical trials of such agents, symptomatic upper GI ulcers, gross bleeding, or perforation appear to occur in approximately 1% of patients treated for 3 to 6 months and in about 2 to 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. FLOCTAFENINE (floctafenine), however, is only recommended for short-term use.

The incidence of these complications increases with increasing dose.

FLOCTAFENINE (floctafenine) should be given under close medical supervision to patients prone to gastrointestinal tract irritation particularly those with a history of peptic ulcer, diverticulosis or other inflammatory disease of the gastrointestinal tract such as ulcerative colitis and Crohn's disease. In these cases the physician must weigh the benefits of treatment against the possible hazards.

Healthcare professionals should inform patients about the signs and/or symptoms of serious GI toxicity and instruct them to contact a healthcare professional immediately if they experience persistent dyspepsia or other symptoms or signs suggestive of gastrointestinal ulceration or bleeding.

If ulceration is suspected or confirmed, or if GI bleeding occurs, FLOCTAFENINE should be discontinued immediately, appropriate treatment instituted and the patient monitored closely.

No studies to date, have identified any group of patients not at risk of developing ulceration and bleeding.

Caution should be taken if prescribing FLOCTAFENINE 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)

Studies to date show that all NSAIDs can cause GI tract adverse events. Although existing data does not clearly identify differences in risk between various NSAIDs, this may be shown in the future.

There is no definitive evidence that the concomitant administration of histamine H_2-receptor antagonists and/or antacids will either prevent the occurrence of gastrointestinal side effects or allow the continuation of FLOCTAFENINE (floctafenine) therapy when and if these adverse reactions appear.

Genitourinary

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

Hematologic

Drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to varying degrees; therefore, 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 FLOCTAFENINE 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 FLOCTAFENINE with warfarin requires close monitoring of the international normalized ratio (INR).

Even with therapeutic INR monitoring, increased bleeding may occur (see 9.4 Drug-Drug Interactions, Anticoagulants).

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.

FLOCTAFENINE 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 9.4 Drug-Drug Interactions, Acetylsalicylic Acid (ASA) or other NSAIDs). Concomitant administration of FLOCTAFENINE 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 non-steroidal anti-inflammatory drugs are rare, but could occur with severe consequences.

Anemia is sometimes seen in patients receiving NSAIDs, including FLOCTAFENINE. 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 FLOCTAFENINE, 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 non-steroidal anti-inflammatory drugs, 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.

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 more severe hepatic reaction while on therapy with this drug. Severe hepatic reactions including jaundice and cases of fatal hepatitis have been reported with non-steroidal anti-inflammatory drugs.

Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop (e.g. jaundice), or if systemic manifestations occur (e.g. eosinophilia, associated with rash, etc.) this drug should be discontinued.

If there is a need to prescribe this drug in the presence of impaired liver function, it must be done under strict observation.

Immune

Infection: FLOCTAFENINE, in common 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 healthcare professional must be vigilant to the development of this complication.

Anaphylactoid Reactions: As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to FLOCTAFENINE. In post-marketing experience, rare cases of anaphylactic/ anaphylactoid reactions and angioedema have been reported in patients receiving FLOCTAFENINE. FLOCTAFENINE should NOT be given to 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 2 CONTRAINDICATIONS).

ASA-Intolerance: FLOCTAFENINE should NOT be given to patients with the complete or partial syndrome of ASA-intolerance (rhinosinusitis, urticaria/angioedema, nasal polyps, asthma) in whom asthma, anaphylaxis, urticaria/angioedema, rhinitis or other allergic manifestations are precipitated by ASA or other non-steroidal anti-inflammatory agents. 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. On occasion, it has been observed that intermittent use may have resulted in increased sensitivity.

Sensitivity and Cross-sensitivity: Avoid occasional repeated dosing which may cause sensitization (notably for some acute pain states). Generalized and mucocutaneous allergic reactions possibly culminating in shock, may occur. These may often be preceded by the appearance of minor allergic symptoms: formication of the palms and soles, sudden reddening of the face and neck, rash, laryngeal tickling sensation and malaise. This type of previous history should be systematically evaluated before each new prescription. It is a contraindication to continuing or resuming treatment with floctafenine either alone or in combination with compounds having a similar chemical structure because of possible cross-sensitivity.

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

Serious skin reactions: See 7 WARNINGS AND PRECAUTIONS, Skin.

Monitoring and Laboratory Tests

Cardiovascular: Patients on long-term treatment with FLOCTAFENINE should have their blood pressure monitored regularly (see 2 CONTRAINDICATIONS, 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Risk of CV Adverse Events, Cardiovascular and 9.4 Drug-Drug Interactions).

Hematology: Hemoglobin, hematocrit, red blood cells (RBCs), white blood cells (WBCs), and platelets should be checked in patients on long-term treatment with FLOCTAFENINE. Additionally, concurrent therapy with anticoagulants requires close monitoring of the international normalized ratio (INR) (see Hematologic and 9.4 Drug-Drug Interactions).

Hepatic: Serum transaminase and bilirubin should be monitored regularly during FLOCTAFENINE therapy (see Hepatic/Biliary/Pancreatic).

Ophthalmologic: Ophthalmologic examinations may be required in patient receiving this drug for an extended period of time (see Ophthalmologic).

Pregnancy: If FLOCTAFENINE is administered in the middle (approximately 20 weeks) to the end of the second trimester, it is recommended that pregnant women on FLOCTAFENINE be closely monitored for amniotic fluid volume since FLOCTAFENINE may result in reduction of amniotic fluid volume and even oligohydramnios (see 7.1.1 Pregnant Women). FLOCTAFENINE is contraindicated for use in the third trimester of pregnancy (see 2 CONTRAINDICATIONS, 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Risk in Pregnancy, and 7.1.1 Pregnant Women).

Renal: Serum creatinine, creatine clearance and serum urea should be checked in patient during FLOCTAFENINE therapy. Electrolytes including serum potassium should be monitored periodically (see 4.2 Recommended Dose and Dosage Adjustment, Renal and 9.4 Drug-Drug Interactions).

Neurologic

Some patients may experience drowsiness, dizziness, vertigo, tinnitus, hearing loss, insomnia with the use of FLOCTAFENINE. If patients experience such adverse reactions, they should exercise caution in carrying out activities that require alertness.

Ophthalmologic

Blurred and/or diminished vision has been reported with the use of FLOCTAFENINE and other non-steroidal anti-inflammatory drugs. If such symptoms develop, FLOCTAFENINE should be discontinued and an ophthalmologic examination performed. Ophthalmologic examination should be carried out at periodic intervals in any patient receiving FLOCTAFENINE for an extended period of time.

Peri-Operative Considerations

See 2 CONTRAINDICATIONS, Coronary Artery Bypass Graft Surgery.

Psychiatric

Some patients may experience depression with the use of NSAIDs, such as FLOCTAFENINE. If patients experience such adverse reaction, they should exercise caution in carrying out activities that require alertness (see Neurologic).

Renal

Long-term administration of non-steroidal anti-inflammatory drugs 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.

Renal insufficiency 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 insufficiency (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 FLOCTAFENINE, 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. Floctafenine and its metabolites are eliminated primarily by the kidneys, therefore the drug should be used with great caution in patients with impaired renal function. In these cases, utilization of lower doses of FLOCTAFENINE should be considered and patients monitored.

In clinical trials with floctafenine, dysuria, without apparent changes in renal function, was reported. The incidence of dysuria was greater in males than in females and occurred primarily in the first morning voiding. It has not been established whether dysuria is related to dose and/or duration of drug administration.

Advanced Renal Disease: See 2 CONTRAINDICATIONS.

Fluid and Electrolyte Balance: Use of NSAIDs, such as FLOCTAFENINE, 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 FLOCTAFENINE in patients with a history of congestive heart failure, compromised cardiac function, hypertension, increased age or other conditions predisposing to fluid retention (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

Use of NSAIDs, such as FLOCTAFENINE, 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 2 CONTRAINDICATIONS).

Reproductive Health: Female and Male Potential

- **Fertility**

  The use of FLOCTAFENINE, 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 FLOCTAFENINE should be considered.

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.

Skin

Serious skin reactions: Use of some NSAIDs, such as FLOCTAFENINE, have been associated with rare postmarket cases of serious, fatal or otherwise life-threatening skin reactions, including:

- drug reaction with eosinophilia and systemic symptoms (DRESS)
- Stevens-Johnson syndrome,
- toxic epidermal necrolysis,
- exfoliative dermatitis and
- erythema multiforme.

Patients appear to be at higher risk for these events early in the course of therapy, with the onset of cases usually occurring within the first month of treatment. These reactions may be reversible if the causative agent is discontinued and appropriate treatment instituted. Patients should be advised that they should discontinue their NSAID at the first appearance of a skin rash, mucosal lesions or any other sign of hypersensitivity, and contact their physician immediately for assessment and advice, including which therapies to discontinue.

DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological

abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection, and eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident.

7.1 Special Populations

7.1.1 Pregnant Women

FLOCTAFENINE is contraindicated for use during the third trimester of pregnancy because of risks of premature closure of the ductus arteriosus and the potential to prolong parturition (see 2 CONTRAINDICATIONS and 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology). Caution is recommended in prescribing FLOCTAFENINE during the first and second trimesters of pregnancy, particularly from the middle to end of the second trimester of pregnancy (onset at approximately 20 weeks) due to possible fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment or failure.

Published studies and postmarketing reports describe maternal NSAID use at approximately 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment or failure. NSAIDs were shown to cause significant reduction in fetal urine production prior to reduction of amniotic fluid volume. There have also been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction and renal impairment without oligohydramnios, some of which were irreversible, even after treatment discontinuation.

These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Complications of prolonged oligohydramnios may for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If after careful consideration of the benefit-risk, NSAID treatment is considered necessary to be administered anywhere from the middle (onset at approximately 20 weeks) to the end of the second trimester of pregnancy, the use should be limited to the lowest effective dose and shortest duration possible. It is also recommended that ultrasound monitoring of amniotic fluid be considered if FLOCTAFENINE treatment extends beyond 48 hours and that NSAIDs treatment be discontinued if oligohydramnios occurs, followed by appropriate medical follow up.

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or 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-fetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenesis period.

As floctafenic acid crosses the placental barrier, the use of FLOCTAFENINE in women of childbearing potential requires that the likely benefit of the drug be weighed against the possible risk to the mother and fetus.

7.1.2 Breast-feeding

It has been shown that floctafenic acid is slightly secreted in breast milk. Therefore, use of FLOCTAFENINE in women who are breastfeeding is not recommended (see 2 CONTRAINDICATIONS).

7.1.3 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of floctafenine in children have not been established and therefore its use in this age group is not recommended.

The safety and efficacy of long-term use of floctafenine have not been clearly established (see 2 CONTRAINDICATIONS).

7.1.4 Geriatrics

Geriatrics (>65 years of age): Patients older than 65 years and frail or debilitated patients are most susceptible to a variety of adverse reactions from non-steroidal anti-inflammatory drugs (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 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.

As with other non-steroidal anti-inflammatory drugs, FLOCTAFENINE should be used with caution in the elderly and consideration given to administration of a lower starting dose (see 7 WARNINGS AND PRECAUTIONS, General).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most common adverse reactions encountered with non-steroidal anti-inflammatory drugs are gastrointestinal, of which peptic ulcer, with or without bleeding, is the most severe. Fatalities have occurred, particularly in the elderly.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed

in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The most commonly occurring side effects reported during FLOCTAFENINE therapy were:

Gastrointestinal disorders: Nausea, diarrhea, vomiting, abdominal pain or discomfort, heartburn, constipation, gastrointestinal bleeding.

General disorders and administration site conditions: Sensation of burning of the face and extremities, sensation of malaise.

Immune system disorders: Cases of anaphylactic shock and angioedema have been reported in clinical use (see 7 WARNINGS AND PRECAUTIONS, Immune).

Hepatobiliary disorders: Abnormal liver function.

Nervous system disorders: Drowsiness, dizziness, headache.

Psychiatric disorders: Insomnia, nervousness, irritability.

Renal and urinary disorders: Dysuria, burning micturition, polyuria, strong smelling urine, urethritis and cystitis. Reversible acute renal insufficiency with or without oliguria/anuria.

Respiratory, thoracic and mediastinal disorders: Asthmatic type dyspnea.

Skin and subcutaneous tissue disorders: Maculopapular skin rash, pruritus, urticaria, redness and itching of the face and neck.

8.3 Less Common Clinical Trial Adverse Reactions

Other less frequently occurring side effects were:

Blood and lymphatic system disorders: Very rarely: thrombocytopenia.

Cardiac disorders: tachycardia

Ear and labyrinth disorders: tinnitus

Eye disorders: blurred vision

Gastrointestinal disorders: dry mouth, bitter taste, stomach cramps, flatulence

General disorders and administration site conditions: thirst, hot flushes and sweating, weakness and tiredness

Metabolism and nutrition disorders: anorexia.

8.5 Post-Market Adverse Reactions

Information is not available.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- **NSAIDs:** The use of FLOCTAFENINE in addition to any other NSAID, including those over-the-counter ones (such as ASA and ibuprofen) is not recommended due to the possibility of additive side effects (see 2 CONTRAINDICATIONS and 9.4 Drug-Drug Interactions, Acetylsalicylic Acid (ASA) or other NSAIDs).
- **Beta-Blocking Drugs:** Associated treatment with beta-blocking drugs is contraindicated; in the event of an anaphylactic-type reaction, such treatment may lead to or aggravate hypotension or shock. These compounds decrease cardiovascular compensatory mechanisms (see 2 CONTRAINDICATIONS).

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 2 - Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Acetylsalicylic Acid (ASA) or other NSAIDs	T	Some NSAIDs (e.g. ibuprofen) 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. Concomitant administration of acetylsalicylic acid results in decreased peak serum concentration of non-steroidal anti-inflammatory drugs and slight increases in both clearance and apparent half-life. The clinical significance of these changes is unknown.	The use of FLOCTAFENINE in addition to any other NSAID, including over-the-counter ones (such as ASA and ibuprofen) for analgesic and/or anti-inflammatory effects is NOT recommended because of the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions. The exception is the use of low dose 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.
Antacids	T	No pharmacokinetic interaction has been noted with concomitant administration of antacids.	

Proper/Common name	Source of Evidence	Effect	Clinical comment
Anticoagulants	CT	Numerous studies have shown that the concomitant use of NSAIDs and anticoagulants increases the risk of GI adverse events such as ulceration and bleeding.	Because prostaglandins play an important role in hemostasis, and NSAIDs affect platelet function, concurrent therapy of FLOCTAFENINE with warfarin requires close monitoring to be certain that no change in anticoagulant dosage is necessary (see 7 WARNINGS AND PRECAUTIONS, Hematologic, Anti-coagulants).
Anti-hypertensives	T	NSAIDs may diminish the anti-hypertensive effect of Angiotensin Converting Enzyme (ACE) inhibitors. 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.
Anti-platelet Agents (including ASA)	T	There is an increased risk of bleeding, via inhibition of platelet function, when antiplatelet agents are combined with NSAIDs, such as FLOCTAFENINE (see 7 WARNINGS AND PRECAUTIONS, Hematologic, Anti-platelet Effects).	

Proper/Common name	Source of Evidence	Effect	Clinical comment
Diuretics	CT	Clinical studies as well as post-marketing observations have shown that NSAIDs can reduce the effect of diuretics. FLOCTAFENINE may cause water retention and therefore could interfere with diuretics in the treatment of hypertension.	
Glucocorticoids	CT	Numerous studies have shown that the concomitant use of NSAIDs and oral glucocorticoids increases the risk of GI side effects such as ulceration and bleeding. This is especially the case in older (>65 years of age) individuals.	
Lithium	T	Non-steroidal anti-inflammatory drugs are known to be extensively bound to serum albumin. This may lead to interaction with lithium.	Caution should be observed regarding possible interaction between FLOCTAFENINE and lithium should they be used concurrently. Monitoring of plasma lithium concentrations is advised when stopping or starting a NSAID, as increased lithium concentrations can occur.
Methotrexate	T	Non-steroidal anti-inflammatory drugs are known to be extensively bound to serum albumin. This may lead to interaction with certain chemotherapeutic agents such as methotrexate.	Caution should be observed regarding possible interaction between FLOCTAFENINE and methotrexate should they be used concurrently.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Oral Hypoglycemics	T	NSAIDs are known to be extensively bound to serum albumin. This may lead to interaction with hypoglycemic agents.	Caution should be observed when these drugs are used concomitantly.
Protein Bound Drugs (anticoagulants, sulfonylureas, hypoglycemic agents, sulfonamides, phenytoin)	T	Non-steroidal anti-inflammatory drugs are known to be extensively bound to serum albumin. This may lead to interaction with anticoagulants, sulfonylureas, hypoglycemic agents, sulfonamides, phenytoin.	Caution should be observed regarding possible interaction between FLOCTAFENINE and any of these protein bound drugs should they be used concurrently.
Selective Serotonin Reuptake Inhibitors (SSRIs)	T	Concomitant administration of NSAIDs and SSRIs may increase the risk of gastrointestinal ulceration and bleeding (see 7 WARNINGS AND PRECAUTIONS, Gastrointestinal).	
Steroids	C		In patients receiving concomitant steroid therapy, any reduction in steroid dosage should be gradual to avoid the possible complications of sudden steroid withdrawal.
Vitamin K Antagonists	C	Changes in prothrombin time have been noted in patients undergoing long-term treatment with vitamin K antagonists and FLOCTAFENINE.	The prothrombin time or INR should be monitored during long-term treatment with FLOCTAFENINE.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

The administration of floctafenine is not known to interfere with laboratory and diagnostic tests.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Floctafenine, an anthranilic acid derivative, is a non-steroidal anti-inflammatory agent with analgesic and anti-inflammatory properties. The analgesic activity is comparable to that of other mild analgesics in the relief of acute pain. Floctafenine has been shown to inhibit *in vitro* biosynthesis of prostaglandins PGE_2 and $PGF_{2\alpha}$. Gastrointestinal bleeding determined by daily fecal blood loss, was shown in one clinical trial to be approximately 1.2 mL after 1600 mg/day of floctafenine compared to 10.4 mL after 2400 mg/day of acetylsalicylic acid.

10.2 Pharmacodynamics

In pharmacological tests, all doses were administered orally unless otherwise stated. Floctafenine has been shown to have analgesic activity in the acetic acid writhing test in mice and the Randall-Selitto test in rats. In the former test, ED_{50}'s of 3.5 mg/kg, 100 mg/kg and 0.65 mg/kg were found for floctafenine, acetylsalicylic acid and indomethacin, respectively. Floctafenine was still effective four hours after treatment. In rats, doses of 10 to 20 mg/kg of floctafenine were comparable to doses of 2 to 10 mg/kg indomethacin.

In the D'Amour-Smith and the hot plate test in mice, floctafenine was inactive, indicating that its analgesic activity is unlike opiate agonists.

The anti-inflammatory activity of floctafenine was studied in 3 tests: U.V.-induced erythema, plantar edema induced by carrageenin and chronic arthritis induced by Freunds adjuvant. The ED_{50}'s for floctafenine, indomethacin and acetylsalicylic acid were 26 mg/kg, 6.7 mg/kg and 170 mg/kg respectively in the first test. In the carrageenin-induced edema, corresponding results were 72 mg/kg, 4.1 mg/kg and 115 mg/kg, respectively. In the chronic arthritis test, floctafenine at a dose of 50 mg/kg/day was only moderately effective, as was acetylsalicylic acid 100 mg/kg/day; floctafenine produced an additive effect to the anti-inflammatory effects of dexamethasone, without inhibition of its own analgesic activity. Studies in isolated guinea-pig ileum have shown floctafenine to be a mild and non-specific antagonist to the spasmogenic effects of bradykinin, serotonin, prostaglandin E_2, histamine and acetylcholine. Floctafenine has been shown to be a powerful inhibitor of the *in vitro* biosynthesis of prostaglandins in guinea-pig lung.

Floctafenine produced only a moderate antipyretic effect in rats made hyperthermic by previous injection of yeast suspensions - doses of 100 and 200 mg/kg being necessary to produce a 1°C fall in temperature.

The possible induction of physical dependence by floctafenine was investigated in morphine-dependent rhesus monkeys and by chronic (28 to day, increasing dose) administration to previously untreated rhesus monkeys. At oral doses up to 2400 mg/kg no alleviation of withdrawal signs was observed, nor did floctafenine produce any signs of withdrawal effects. The ulcerogenic activity of single doses of floctafenine in starved rats (gastric ulcer) and fed rats (intestinal ulcer) was evaluated at doses up to 500 and 600 mg/kg, respectively. No gastric ulceration was found at doses up to 50 mg/kg; the 100% ulcerogenic dose was 470, 170 and 12 mg/kg for floctafenine, acetylsalicylic acid and indomethacin, respectively. Intestinal lesions were produced at doses above 50 mg/kg, reaching the 100% level at 600 mg/kg. Acetylsalicylic acid was without ulcerogenic activity in this test whereas the U.D. 100 for indomethacin was 15 mg/kg. Floctafenine does not possess any intrinsic anticoagulant activity; it inhibits the action of warfarin when administered concomitantly to animals but potentiates it when administered to an established warfarin therapy.

10.3 Pharmacokinetics

Absorption

The pharmacokinetics and metabolism of ^{14}C-floctafenine were studied in man, mice, rats and dogs. Its absorption, which is exclusively intestinal, is good in man and rodents but only partial in dogs. Floctafenine is rapidly hydrolysed in the liver to floctafenic acid, which becomes the main circulating product.

In normal volunteers, floctafenine was well absorbed after oral administration and peak plasma levels of floctafenic acid, the active metabolite, were attained 1 to 2 hours after administration and declined in a biphasic manner, with an initial (α phase) half-life of approximately 1 hour and a later (β phase) half-life of approximately 8 hours.

Distribution

Only negligible quantities cross the blood-brain barrier, indicating that the analgesic activity is

exclusively peripheral.

Metabolism

In rats, the enzymes responsible for biotransformation are induced by phenobarbital. Plasma concentrations of floctafenine and floctafenic acid during chronic administration to healthy volunteers did not demonstrate any appreciable change in pharmacokinetics with time. Plasma equilibrium was reached after 3 days.

Floctafenine and its metabolites do not accumulate following oral administration of multiple doses in normal volunteers.

Elimination

Elimination of floctafenine and its metabolites is virtually complete 24 hours after administration. Biliary excretion is considerable in mice and man and largely preponderant in rats and dogs. There is no appreciable enterohepatic cycle. Floctafenic acid is the major metabolite but a secondary route, common to all species, leads to hydroxylation in the para-position to the anthranilic nitrogen, giving the corresponding phenols. In man and rats, floctafenine and its 3 metabolites are excreted mainly in the form of ether and/or ester o-glucuronides.

After oral and intravenous administration of ^{14}C labelled floctafenine, urinary excretion accounted for 40% and fecal and biliary excretion accounted for 60% of the recovered radioactivity. The main urinary metabolites are floctafenic acid and its conjugate with minimal amounts of free floctafenine.

Special Populations and Conditions

- **Pediatrics:** The safety and efficacy of floctafenine in children have not been established and therefore its use in this age group is not recommended (see 7.1.3 Pediatrics).
- **Geriatrics:** Floctafenine should be used with caution in the elderly and consideration given to administration of a lower starting dose (see 7.1.4 Geriatrics).
- **Sex:** The clinical trial data on which the indication was originally authorized is not available.
- **Pregnancy and Breast-feeding:** Floctafenine is contraindicated in third trimester of pregnancy and breast-feeding women (see 7.1.1 Pregnant Women and 7.1.2 Breast-feeding).
- **Genetic Polymorphism:** The clinical trial data on which the indication was originally authorized is not available.
- **Ethnic Origin:** The clinical trial data on which the indication was originally authorized is not available.
- **Hepatic Insufficiency:** See 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic.
- **Renal Insufficiency:** See 7 WARNINGS AND PRECAUTIONS, Renal.
- **Obesity:** The clinical trial data on which the indication was originally authorized is not

available.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15°C to 30°C). Protect from light.

FLOCTAFENINE should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended.

12 SPECIAL HANDLING INSTRUCTIONS

None.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

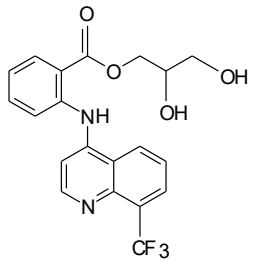
Drug Substance

Proper name: Floctafenine

Chemical name: 2,3-dihydroxypropyl-N-(8-trifluromethyl-4-quinolyl) anthranilate

Molecular formula and molecular mass: $C_{20}H_{17}F_3N_2O_4$ and 406.37 g/mol

Structural formula:



Physicochemical properties: Floctafenine is a pale yellow powder with a melting point of 175-179°C. It is soluble in alcohol, acetone; very slightly soluble in ether, chloroform and methylene chloride and insoluble in water.

14 CLINICAL TRIALS

14.2 Comparative Bioavailability Studies

A comparative bioavailability study was performed on healthy human volunteers. The rate and extent of absorption of floctafenine was measured and compared following oral administration of 2 x 400 mg of either FLOCTAFENINE 400 mg tablets or Idarac 400 mg tablets. The results from measured data are summarized as follows:

Summary Table of the Comparative Bioavailability Data Floctafenine (Dose: 2 x 400 mg) From Measured Data - Under Fasting Conditions		
Parameter	**Geometric Mean** **Arithmetic Mean (CV%)**	**Ratio of Geometric Means (%)****

	FLOACTAFEINE	Idarac®†	
AUC_T (mcg·hr/mL)	27.5 29.6 (37)	27.2 28.9 (39)	100.6
AUC_I (mcg·hr/mL)	32.6 35.2 (39)	34.4 36.7 (38)	9.4
C_{max} (mcg/mL)	7.81 8.66 (38)	6.72 7.79 (74)	116.0
T_{max} (hr)*	1.35 (47)	1.28 (50)	
$t_{1/2}$ (hr)*	22.1 (89)	22.3 (61)	

* Arithmetic means (CV%).

** Based on the least squares estimate.

† Idarac® is manufactured by Sanofi Canada Inc., formerly Sanofi Winthrop, and was purchased in Canada.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Floctafenine was investigated for acute toxicity orally in mouse, rat and rabbit: respective LD_{50} values were 2.83 g/kg, 1.03 g/kg and 700 mg/kg. Intravenous and intraperitoneal LD_{50} values in mice were 192 mg/kg and 395 mg/kg.

In a 6-month chronic toxicity study, groups of 30 male and 30 female rats were given floctafenine, 0, 20, 80 or 160 mg/kg/day by esophageal tube.

After 4 and 13 weeks of treatment, a moderate decrease in the number of erythrocytes and hemoglobin concentration was noted. This had progressed to reactive polycythemia, more marked in males than females, by the 26th week. Similar, but more pronounced effects were seen in the group given 160 mg/kg. 7 deaths occurred and at the 4 and 13-week stages, a decrease in total proteins, hyperleucocytosis and moderate anemia were also seen. Autopsy and histological examination of the organs did not reveal any signs of toxicity, which could be attributed to the drug. In a 6-month chronic toxicity study in beagle dogs, groups of 3 males and 3 females were given doses of 0, 50, 150 and 450 mg/kg/day of floctafenine. In the two higher dosage groups, a slight to moderate, dose-related, increase in erythrocyte sedimentation rate was seen, which was more marked in males than in females. Areas of ulceration in the pyloric region, accompanied by a reaction process indicative of the beginning of reparation, were seen in 2 dogs dosed at 150 mg/kg and in 5 dogs at 450 mg/kg.

In a long-term toxicity study, groups of 65 male and 65 female Charles River CD rats were fed floctafenine in the diet at doses of 0, 20, 60 and 180 (increased to 240 after 27 weeks) mg/kg/day. At the highest dose, survival rate was reduced in females and body weight gain, but not food intake, was decreased in both sexes. There was an increased water intake and urinary volume, accompanied in males only by a decrease in specific gravity of the urine and an increased incidence of haematuria. Urea concentrations were increased in females after 78 weeks, and in males at both 240 mg/kg/day and 60 mg/kg/day after 103 weeks. Alkaline phosphatase levels were increased in the high dose males after 78 weeks. From week 54 onwards, reduced erythrocytic characteristics and from week 72 onwards, increased leucocyte and thrombocyte numbers were seen in both sexes at 240 mg/kg/day. At autopsy increased organ weights of liver, spleen and kidney at 240 mg/kg/day and of kidney in males only at 60 mg/kg/day were seen. Some rats in the high dose group revealed ulcerative changes in the large intestine, which were considered to have led to peritonitis, cystic changes in the mesenteric lymph nodes and liver abscess. There was also slight exacerbation of the renal lesions normally seen in the CD rat. The incidence and range of neoplasms remained unaltered.

A one-year chronic toxicity study in beagle dogs (3 males, 3 females per group) at floctafenine doses of 0, 50, 100, 200 and 400 mg/kg/day was performed. Two deaths occurred during treatment; a female dog in the highest dose group died during week 28 due to a drug-induced effect upon the gastrointestinal tract; a male dog in the lowest dose group was sacrificed due to weakness resulting from cystitis and pyelonephritis, not considered to be treatment related. Animals in both the higher dose groups showed signs of anemia and gastrointestinal disturbances, with diarrhea and fecal blood loss, of dose-related severity. The incidence of these signs decreased after some weeks of treatment. Only slight changes in the intestinal tract were seen at necropsy. No effects were seen at doses of 100 and 50 mg/kg/day.

A repeat study using 4 male and 4 female dogs per group and doses of 50, 150 and 400 mg/kg/day was performed. No drug-related deaths occurred. A small reduction in erythrocytic parameters was detected in 4 dogs at 400 mg/kg/day. Reduced total serum protein values were seen on occasions, in females only, at doses of 150 and 400 mg/kg/day. Serum levels of floctafenine in these animals peaked at 1 to 6 hours after dosing, ranging from 4 to 18, 1 to 26 and 4 to 41 :g/mL for the low, intermediate and high dosage groups respectively, and falling to approximately 4 :g/mL after 24 hours.

Carcinogenicity

An 8-week oncogenicity appraisal in CD-1 mice receiving 0, 20, 80 and 240 mg/kg/day of floctafenine did not reveal any significant change in the incidence of neoplasms. The growth rate of male mice receiving the highest dose was reduced from the 17th week onwards. In 11 of those mice dying in this group, fibrous exudate or adhesions in the abdominal cavity indicated a relation to treatment with floctafenine.

Genotoxicity

Information is not available.

Reproductive and Developmental Toxicology

The study of the possible teratogenic effects of floctafenine was carried out in mice, rats and rabbits treated orally with the drug during gestation. The doses administered to mice, were 80, 160 and 320 mg/kg/day; to rats, 40, 80, 160 and 240 mg/kg/day; and to rabbits, 40, 80 and 160 mg/kg/day. Four mice treated at 320 mg/kg/day died (1 on day 11, 3 on day 17).

The rate of fetal losses in the highest dosage group of mice was 24% compared to 3% in the controls; the difference was statistically significant at $p<0.01$. No teratogenic effect was observed.

Floctafenine did not have any adverse effect upon the progress of gestation in rats; in high doses it produced a diminution of the mean fetal weight. No teratogenic effects were observed.

In rabbits, fetal losses were 19% in the highest dosage group, compared to 5.9% in control animals; no teratogenic effects were observed. A second study in the rabbit at doses of 25, 50 and 100 mg/kg/day did not adversely affect litter size, fetal loss, litter and mean pup weights or produce any teratogenic effects.

In a study of fertility and breeding capacity, Sprague-Dawley rats were dosed at 40, 80 and 160 mg/kg/day for ten weeks before mating and, in females, throughout gestation and lactation. There were no differences in fertility between control and treated animals. The breeding capacity of the treated animals remained the same as the controls and no deformed animals were born.

Special Toxicology

Information is not available.

Juvenile Toxicity

Information is not available.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrFLOCTAFENINE

Floctafenine Tablets

Read this carefully before you start taking **FLOCTAFENINE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **FLOCTAFENINE**.

Serious Warnings and Precautions

Heart and blood vessel problems:

- FLOCTAFENINE can cause heart and blood vessel problems like heart attacks, stroke, blood clots, high blood pressure and heart failure. These can lead to death.
- The risk of having heart problems is higher if you take FLOCTAFENINE for long periods of time and/or at higher doses and/or in people who have heart disease.
- Tell your healthcare professional if you have or had heart attacks, chest pain, heart disease, stroke, heart failure, high blood pressure or diabetes.

Stomach and intestine (gastrointestinal) problems:

- FLOCTAFENINE can cause stomach and intestine problems like ulcers, inflammation, bleeding, holes/perforation, blockage or pain.

Pregnancy:

- **DO NOT** take FLOCTAFENINE if you are pregnant and in a later stage of pregnancy (28 weeks or later).
- If you are pregnant and in an earlier stage of pregnancy (less than 28 weeks) **only** take FLOCTAFENINE if you are told to do so by your healthcare professional.
- Medicines like FLOCTAFENINE may cause harm to you and your baby. Your healthcare professional will need to closely monitor your health and that of your baby (including your amniotic fluid levels) if they prescribe FLOCTAFENINE during this time.
- Tell your healthcare professional right away if you become pregnant, think you may be pregnant or want to get pregnant during your treatment with FLOCTAFENINE.

What is FLOCTAFENINE used for?

FLOCTAFENINE is used in adults for a short time to relieve mild to moderate pain.

How does FLOCTAFENINE work?

FLOCTAFENINE belongs to a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs). It can reduce the chemicals produced by your body which causes pain and swelling.

FLOCTAFENINE only treats the symptoms and relieves pain and inflammation as long as you take it. FLOCTAFENINE does not cure the illness or stop it from getting worse.

What are the ingredients in FLOCTAFENINE?

Medicinal ingredient: Floctafenine

Non-medicinal ingredients: Colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose and stearic acid.

FLOCTAFENINE comes in the following dosage forms:

Tablets: 200 mg and 400 mg.

Do not use FLOCTAFENINE if:

- You have heart bypass surgery (planning to have or recently had).
- You have severe, uncontrolled heart failure.
- You have bleeding in the brain or other bleeding disorders.
- You are pregnant and in a later stage of pregnancy (28 weeks or later).
- You are currently breastfeeding or planning to breastfeed.
- You are allergic to floctafenine or any other ingredients in FLOCTAFENINE or the container.
- You have a history of asthma, hives, growths in your nose, sinus swelling or symptoms of an allergic reaction after taking acetylsalicylic acid (ASA) or other NSAIDs.
- You have active stomach or intestinal ulcers.
- You have active bleeding from the stomach or gut.
- You have inflammatory bowel disease (Crohn's Disease or Ulcerative Colitis).
- You have liver disease (active or severe).
- You have kidney disease (severe or worsening).
- You have high potassium in the blood.
- You are taking:
    - other NSAIDs, used to treat pain, fever and inflammation.
    - beta blockers, used to treat heart problems.
- You are under 18 years of age.
- You have coronary artery disease.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take FLOCTAFENINE. Talk about any health conditions or problems you may have, including if you:

- have a condition that makes you frail or weak.
- have or have had heart attacks, chest pain, heart disease, stroke or heart failure.
- have a history of ulcer or bleeding from the stomach or gut (small or large intestine).
- have a stomach infection.
- have liver or kidney problems, urine problems or are dehydrated.
- have asthma and have growths in your nose (nasal polyps).

- have poor blood flow to your extremities (like your hands and feet).
- smoke or used to smoke.
- drink a lot of alcohol.
- have high blood pressure, high cholesterol or diabetes.
- have other bleeding or blood problems.
- have immune system problems.
- are pregnant, planning on becoming or become pregnant while taking FLOCTAFENINE.
- are taking any other medicines.
- are on a low-sodium diet.

Other warnings you should know about:

FLOCTAFENINE may cause serious side effects, including:

- **Blood and bleeding problems**:
  - FLOCTAFENINE can cause blood problems, bleeding and prolonged bleeding.
  - Taking FLOCTAFENINE with the following medicines can increase the risk of bleeding:
    - anticoagulants (prevents blood clots), corticosteroids (anti-inflammatory), or antidepressants like selective serotonin reuptake inhibitors (SSRIs).
- **Aseptic meningitis** (inflammation of the protective lining of the brain that is not caused by an infection): Patients with autoimmune disorders are at a higher risk.
- **Serious Skin Reactions:** In rare cases, serious or life-threatening skin reactions listed below have been reported with some NSAIDs, such as FLOCTAFENINE.
  - Drug reaction with eosinophilia and systemic symptoms (DRESS)
  - Stevens-Johnson syndrome (SJS),
  - toxic epidermal necrolysis (TEN),
  - exfoliative dermatitis and
  - erythema multiforme

  You may be at a greater risk of experiencing a serious skin reaction usually during the first month of treatment. See the Serious side effects and what to do about them table, below, for more information on these and other serious side effects.

Infection: FLOCTAFENINE may mask signs of an infection such as fever or muscle aches. If you notice other symptoms of infection (e.g., painful or frequent urination, sore throat, cough), tell your healthcare professional.

Surgery: Tell any healthcare professional that you see, that you are taking this medicine. This is especially important if you are planning to have heart surgery.

Fertility in women: FLOCTAFENINE may affect your fertility. This means that it may be difficult for you to have a child. If you have trouble having a child, you might need to stop taking FLOCTAFENINE. Talk to your healthcare professional if you have any questions about this.

Adults (65 years or older): Side effects like gastrointestinal problems may happen more often. Your healthcare professional might have you start with a lower dose of FLOCTAFENINE. They will monitor your health during and after treatment.

Driving and using machinery: FLOCTAFENINE may cause eye or nervous system problems. This includes tiredness, trouble sleeping, blurred vision, spinning or dizziness (vertigo), hearing problems or depression. Be careful about driving or doing activities that require you to be alert. If you become drowsy, dizzy or light-headed after taking FLOCTAFENINE, do NOT drive or operate machinery.

Check-ups and testing: You will have regular visits with your healthcare professional during treatment with FLOCTAFENINE to monitor your health. They will:

- Check your blood pressure.
- Check your eyes. FLOCTAFENINE can cause blurred or reduced vision.
- Do blood and urine tests to check your liver, kidney and blood health.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions

Do not take FLOCTAFENINE with:

- acetylsalicylic acid (ASA) or other NSAIDs, used to treat pain, fever and inflammation (such as celecoxib, diclofenac, ibuprofen, indomethacin, ketorolac, meloxicam, naproxen);
- Beta-blockers, used to treat heart problems.

Taking FLOCTAFENINE with these medicines may cause serious drug interactions. Ask your healthcare professional if you are unsure you are taking these medicines.

The following may interact with FLOCTAFENINE:

- Corticosteroids (including glucocorticoids such as prednisone), used to treat inflammation.
- Lithium, used to treat mental illness.
- Medicines used to treat depression called Selective Serotonin Reuptake Inhibitors (such as citalopram, fluoxetine, paroxetine, and sertraline).
- Medicines used to treat high blood pressure, like enalapril, lisinopril, perindopril, ramipril, candesartan, irbesartan, losartan, and valsartan.
- Medicines used to lower extra fluid levels (diuretics), like furosemide, and hydrochlorothiazide.
- Medicines used as blood thinners or to prevent blood clots, like warfarin, clopidogrel, heparin, and dextrans.

- Medicines used to control certain types of seizures, like phenytoin.
- Methotrexate, used to treat different cancers.
- Medicines used to treat diabetes, like sulfonylureas or other oral hypoglycaemics like glibenclamide, metformin, chlorpropamide or phenformin, tolbutamide.
- Medicines used to treat bacterial infections (antibiotics), like sulphonamide.
- Vitamin K Antagonists used to prevent blood clotting.

How to take FLOCTAFENINE:

- Take FLOCTAFENINE exactly as your healthcare professional has told you. They should recommend the lowest dose possible for your treatment for the shortest time needed.
- To lessen stomach upset, take this medicine immediately after a meal or food. Swallow the tablets with a glass of water. If stomach upset (indigestion, nausea, vomiting, stomach pain or diarrhea) occurs and continues, contact your healthcare professional.
- You should remain standing or sitting upright for about 15 to 30 minutes after taking this medicine. This helps to prevent irritation that may lead to trouble swallowing.
- **This medicine has been prescribed specifically for you. Do not give it to anyone else. It may harm them, even if their symptoms seem similar to yours.**

Usual dose:

Adults (18 years of age and older):

- Your healthcare professional will decide on the best dosage for you based on your condition, age and health of your kidneys.
- Your healthcare professional may lower your dose, stop your treatment for a period of time or recommend that you stop your treatment completely. This may happen if you:
  - experience serious side effects, or
  - your disease gets worse.

Overdose:

If you think you, or a person you are caring for, have taken too much FLOCTAFENINE, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

- If you miss a dose of FLOCTAFENINE, take the dose as soon as you remember. Take your next dose at the usual time.
- If it is almost time for your next dose, skip the missed dose. Take your next dose at the usual time.
- Do NOT double your dose to make up the missed dose.

What are possible side effects from using FLOCTAFENINE?

These are not all the possible side effects you may have when taking FLOCTAFENINE. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- nausea, diarrhea, vomiting, stomach upset, heartburn, constipation, indigestion, feeling gassy
- feeling of burning of the face and extremities
- drowsiness, dizziness, headache
- trouble sleeping, nervousness, irritability
- thirst, dry mouth, changes in tastes
- skin rash, itching, hives
- redness and itching of the face and neck
- feeling discomfort
- hot flushes and increased sweating
- weakness, tiredness

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Allergic Reaction: difficulty swallowing or breathing, wheezing, feeling sick to your stomach and throwing up, hives or rash, swelling of the face, lips, tongue or throat			√
Cystitis (bladder infection): increased need to urinate, pain in the pelvis or lower back, frequent urination during the night, cloudy urine that may contain blood, burning sensation when passing urine		√	
Gastrointestinal (GI) problems (bleeding, blockage, holes, ulcers or inflammation in your GI tract): blood in vomit, black tarry or bloody stool, dizziness, stomach pain, bloating, loss of appetite, weight loss, nausea, vomiting, constipation or			√

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
diarrhea, chills or fever			
Kidney problems: nausea, vomiting, fever, swelling of extremities, fatigue, thirst, dry skin, irritability, dark urine, increased or decreased urine output, blood in the urine, rash, weight gain (from retaining fluid), loss of appetite, abnormal blood test results, mental status changes (drowsiness, confusion, coma)			√
Lung problems (asthma): increased shortness of breath, wheezing, difficulty breathing, cough and chest tight ness, irregular heartbeat		√	
UNCOMMON			
Anorexia (an eating disorder): fear of gaining weight, unusual eating behaviours, altered body image	√		
Blood problems (low white and/or red blood cell or platelet count): feeling tired or weak, pale skin, bruising or bleeding for longer than usual if you hurt yourself, fever, chills		√	
Blurred vision		√	
Tachycardia (abnormally fast heartbeat): dizziness, light headedness, shortness of breath, racing heart		√	
Tinnitus: ringing, buzzing, clicking or hissing in the ears		√	
RARE			
Aseptic meningitis (inflammation of the protective lining of the brain that is not		√	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
caused by infection): headaches, stiff neck, nausea and vomiting, fever or clouding of consciousness			
Congestive Heart Failure (heart does not pump blood as well as it should)**:** shortness of breath, fatigue and weakness, swelling in ankles, legs and feet, cough, fluid retention, lack of appetite, nausea, rapid or irregular heartbeat, reduced ability to exercise			√
Depression (sad mood that won't go away): difficulty sleeping or sleeping too much, changes in appetite or weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, family, gatherings and activities with friends, reduced libido (sex drive) and thoughts of death or suicide. If you have a history of depression, your depression may become worse		√	
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse or heart palpitations	√		
Myocardial infarction (heart attack): pressure or squeezing pain in the chest, jaw, left arm, between the shoulder blades or			√

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
upper abdomen, shortness of breath, dizziness, fatigue, light-headedness, clammy skin, sweating, indigestion, anxiety, feeling faint and possible irregular heartbeat			
Serious Skin Reactions: fever, severe rash, swollen lymph glands, flu-like feeling, blisters and peeling skin that may start in and around the mouth, nose, eyes and genitals and spread to other areas of the body, swelling of face and/or legs, yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, feeling thirsty, urinating less often, less urine or dark urine			√
Stroke: sudden numbness or weakness of your arm, leg or face, especially if only on one side of the body; sudden confusion, difficulty speaking or understanding others; sudden difficulty in walking or loss of balance or coordination; suddenly feeling dizzy or sudden severe headache with no known cause			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store FLOCTAFENINE at room temperature (15°C to 30°C) and protected from light.

Keep out of reach and sight of children.

Do NOT keep outdated medicine or medicine no longer needed. Return any outdated or unused medicine to your healthcare professional.

If you want more information about FLOCTAFENINE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (https://www.aapharma.ca/en/), or by calling 1-877-998-9097.

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