

**PRODUCT MONOGRAPH**

**FLOCTAFENINE**

**Floctafenine Tablets**

**200 mg and 400 mg**

**Anti-inflammatory, Analgesic**

**AA PHARMA INC.  
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**PRODUCT MONOGRAPH**

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**THERAPEUTIC CLASSIFICATION**

Anti-inflammatory, Analgesic

**ACTIONS AND CLINICAL PHARMACOLOGY**

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<sub>2</sub> and PGF<sub>2α</sub>. 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.

In normal volunteers, floctafenine was well absorbed after oral administration and peak plasma levels of floctafenic acid, the active metabolite, were attained 1-2 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. Floctafenine and its metabolites do not accumulate following oral administration of multiple doses.

After oral and intravenous administration of <sup>14</sup>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.

### Comparative Bioavailability

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 (%)**
	FLOCTAFENE	Idarac <sup>®</sup> †	
AUC <sub>T</sub> (mcg•hr/mL)	27.5 29.6 (37)	27.2 28.9 (39)	100.6
AUC <sub>I</sub> (mcg•hr/mL)	32.6 35.2 (39)	34.4 36.7 (38)	94.4
C <sub>max</sub> (mcg/mL)	7.81 8.66 (38)	6.72 7.79 (74)	116.0
T <sub>max</sub> (hr)*	1.35 (47)	1.28 (50)	
t <sub>1/2</sub> (hr)*	22.1 (89)	22.3 (61)	
* Arithmetic means (CV%).			
** Based on the least squares estimate.			
† Idarac <sup>®</sup> is manufactured by Sanofi Canada Inc., formerly Sanofi Winthrop, and was purchased in Canada.			

### **INDICATIONS AND CLINICAL USE**

FLOCTAFENINE (floctafenine) is indicated for short-term use in acute pain of mild and moderate severity.

## **CONTRAINDICATIONS**

The following are contraindications to the use of FLOCTAFENINE (floctafenine):

1. Active peptic ulcer, a history of recurrent ulceration or active inflammatory disease of the gastrointestinal system.
2. Known or suspected hypersensitivity to the drug or other non-steroidal anti-inflammatory drugs. The potential for cross-reactivity between different NSAIDs must be kept in mind.

FLOCTAFENINE should not be used in patients with the complete or partial syndrome of nasal polyps, or in whom asthma, anaphylaxis, urticaria, 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 effects.

3. 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.

4. Significant hepatic impairment or active liver disease.

5. Severely impaired or deteriorating renal function (creatinine clearance <30 mL/min).

Individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed NSAIDs and must be monitored.

6. 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.
7. Severe heart failure.
8. Coronary heart disease.
9. Associated treatment with beta-blocking agents (see PRECAUTIONS – Drug Interactions).

### **WARNINGS**

#### **Gastrointestinal System (GI)**

Serious GI toxicity, such as peptic ulceration, perforation and gastrointestinal bleeding, sometimes severe and occasionally fatal can occur at any time, with or without 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. Physicians should remain alert for ulceration and bleeding in patients treated with non-steroidal anti-inflammatory drugs, even in the absence of previous GI tract 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 3-6 months and in about 2-4% of patients treated for one year. The risk continues beyond one year and possibly increases. 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.

Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and instruct them to contact a physician 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. A prior history of serious GI events and other factors such as excess alcohol intake, smoking, age, female gender and concomitant oral steroid and anti-coagulant use have been associated with increased risk.

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.

#### Use in the Elderly

Patients older than 65 years and frail or debilitated patients are most susceptible to a variety of adverse events 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. See "PRECAUTIONS" for further advice.

#### 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.

#### Aseptic Meningitis

In occasional cases, 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 physician must be vigilant to the development of this complication.

### Use in Pregnancy, Labour and Lactation

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.

It has been shown that floctafenic acid is slightly secreted in breast milk. Therefore, use of FLOCTAFENINE in women who are nursing is not recommended.

### Use in Children

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.

## **PRECAUTIONS**

### Gastrointestinal System

There is no definitive evidence that the concomitant administration of histamine H<sub>2</sub>-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.

## Renal Function

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 with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to the reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of a non-steroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and 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, and the elderly. Discontinuation of non-steroidal anti-inflammatory therapy is usually followed by recovery to the pre-treatment state.

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.

### Genitourinary Tract

Some NSAIDs are known to cause 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, treatment with FLOCTAFENINE must be stopped immediately to obtain recovery. This should be done before any urological investigations or treatments are carried out.

### Hepatic Function

As with other non-steroidal anti-inflammatory drugs, borderline elevations of one or more liver function tests 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 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, or if systemic manifestations occur (e.g. eosinophilia, 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.

### Fluid and Electrolyte Balance

Fluid retention and edema have been observed in patients treated with floctafenine. Therefore, as with many other non-steroidal anti-inflammatory drugs, the possibility of precipitating congestive heart failure in elderly patients or those with compromised cardiac function should be borne in mind. FLOCTAFENINE should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention.

With non-steroidal anti-inflammatory treatment, there is a potential risk of hyperkalemia, particularly in patients with conditions such as diabetes mellitus or renal failure; elderly patients; or in patients receiving concomitant therapy with  $\beta$ -adrenergic blockers, angiotensin converting enzyme inhibitors or some diuretics.

### Hematology

Drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to varying degrees; therefore, patients who may be adversely affected by such an action should be carefully observed when FLOCTAFENINE is administered.

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.

### Infection

In common with other anti-inflammatory drugs, FLOCTAFENINE may mask the usual signs of infection.

### Ophthalmology

Blurred and/or diminished vision has been reported with the use of floctafenine and other non-steroidal anti-inflammatory drugs. If such symptoms develop, this drug should be discontinued and an ophthalmologic examination performed.

### Central Nervous System

Some patients may experience drowsiness, dizziness, vertigo, insomnia or depression with the use of floctafenine. If patients experience these side effects, they should exercise caution in carrying out activities that require alertness.

### Hypersensitivity Reactions

Floctafenine should not be used in patients with the complete or partial syndrome of nasal polyps, or in whom asthma, anaphylaxis, urticaria, 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 effects. On occasion, it has been observed that intermittent use may have resulted in increased sensitivity.

### Cardiovascular Function

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

### Use in Elderly

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 WARNINGS.)

### Drug Interactions

Acetylsalicylic Acid (ASA) or other 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.

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.

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.

Anticoagulants: 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.

Oral Hypoglycemics: NSAIDs are known to be extensively bound to serum albumin. This may lead to interaction with hypoglycemic agents; therefore, caution should be observed when these drugs are used concomitantly.

Diuretics: Floctafenine may cause water retention and therefore could interfere with diuretics in the treatment of hypertension.

Vitamin K Antagonists: 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.

Glucocorticoids: 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.

Antacids: No pharmacokinetic interaction has been noted with concomitant administration of antacids.

Methotrexate: See Other Drug Interactions below.

Lithium: See Other Drug Interactions below.

Other Drug Interactions: 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, lithium and certain chemotherapeutic agents such as methotrexate. Therefore, caution should be observed regarding possible interaction between floctafenine and any of these drugs should they be used concurrently.

In patients receiving concomitant steroid therapy, any reduction in steroid dosage should be gradual to avoid the possible complications of sudden steroid withdrawal.

Clinical Laboratory Tests: The administration of floctafenine is not known to interfere with laboratory and diagnostic tests.

### **ADVERSE REACTIONS**

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.

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

Gastrointestinal System: Nausea, diarrhea, vomiting, abdominal pain or discomfort, heartburn, constipation, abnormal liver function, gastrointestinal bleeding.

Allergic-Type Reactions: Maculopapular skin rash, pruritus, urticaria, redness and itching of the face and neck. Cases of anaphylactic shock and angioedema have been reported in clinical use (see WARNINGS). Sensation of burning of the face and extremities, asthmatic type dyspnea, sensation of malaise.

Central Nervous System: Drowsiness, dizziness, headache, insomnia, nervousness, irritability.

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

Other less frequently occurring side effects were: tinnitus, blurred vision, dry mouth, thirst, bitter taste, anorexia, stomach cramps, flatulence, hot flushes and sweating, tachycardia, weakness and tiredness. Very rarely: thrombocytopenia.

### **SYMPTOMS AND TREATMENT OF OVERDOSE**

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.

### **DOSAGE AND ADMINISTRATION**

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.

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

Elderly and Debilitated: 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.

Children: FLOCTAFENINE is not recommended for use in children.

Other special Precautions: Adults with renal insufficiency – serum levels are slightly elevated and the dose may therefore be reduced.

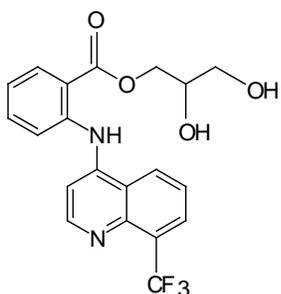
## **PHARMACEUTICAL INFORMATION**

### Drug Substance

Proper/Common Name: floctafenine

Chemical Name: 2,3-dihydroxypropyl-N-(8-trifluoromethyl-4-quinolyl) anthranilate

Structural Formula:



Molecular Formula: C<sub>20</sub>H<sub>17</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub>

Molecular Weight: 406.37

Description: 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.

### Composition

In addition to floctafenine, each tablet contains the non-medicinal ingredients microcrystalline cellulose, croscarmellose sodium, stearic acid, magnesium stearate and colloidal silicon dioxide.

### Stability and Storage recommendations

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

### **AVAILABILITY OF DOSAGE FORMS**

FLOCTAFENINE 200 mg: each creamy white, round, biconvex tablet engraved "FLO" over "200" on one side, 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, contains 400 mg floctafenine. Available in bottle of 100 tablets.

FLOCTAFENINE is a Schedule F (prescription) drug.

### **INFORMATION FOR THE PATIENT**

FLOCTAFENINE, which has been prescribed to you by your doctor, is one of a large group of non-steroidal anti-inflammatory drugs (also called NSAIDs) and is used to relieve mild to moderate acute pain in conditions such as muscle or joint strains or damage, or after a tooth extraction. FLOCTAFENINE helps to relieve pain and swelling by reducing the production of certain substances (prostaglandins) and by helping to control inflammation. NSAIDs promote suppression of the inflammation and the tissue damaging effects resulting from inflammation. This medicine will help you only as long as you continue to take it.

You should take FLOCTAFENINE only as directed by your doctor. Do not take more of it, do not take it more often and do not take it for a longer period of time than your doctor or dentist has ordered. Taking too much of any of these medicines may increase the chance of unwanted effects, especially if you are an elderly patient.

Be sure to take FLOCTAFENINE regularly as prescribed. During treatment, your doctor may decide to adjust the dosage according to your response to the medication.

**STOMACH UPSET IS ONE OF THE COMMON PROBLEMS WITH NSAIDs:**

To lessen stomach upset, take this medicine immediately after a meal or with food, with a glass of water. Also, you should remain standing or sitting upright (i.e. do not lie down) for about 15-30 minutes after taking the medicine. This helps to prevent irritation that may lead to trouble swallowing. If stomach upset (indigestion, nausea, vomiting, stomach pain or diarrhea) occurs and continues, contact your doctor.

Do not take ASA (acetylsalicylic acid), ASA-containing compounds or other drugs used to relieve symptoms of arthritis while taking FLOCTAFENINE unless directed to do so by your physician.

**Always remember: the risks of taking this medication must be weighed against the benefits it will have. Before taking this medication, tell your doctor and pharmacists if you:**

- or a family member are allergic to or have had a reaction to FLOCTAFENINE or other anti-inflammatory drugs (such as acetylsalicylic acid (ASA), diclofenac, diflunisal, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, piroxicam, tiaprofenic acid,

tolmetin, nabumetone or tenoxicam) manifesting itself by increased sinusitis, hives, the initiating or worsening of asthma or anaphylaxis (sudden collapse);

- or a family member has had asthma, nasal polyps, chronic sinusitis or chronic urticaria (hives);
- have a history of stomach upset, peptic ulcer or any other active inflammatory disease of the gastrointestinal tract, liver or kidney diseases;
- have blood or urine abnormalities;
- have high blood pressure;
- have diabetes;
- are on any special diet, such as a low-sodium or low-sugar diet.
- are pregnant or intend to become pregnant while taking this medication;
- are breast feeding or intend to breast feed while taking this medication;
- are taking any other medication (either prescription or non-prescription) such as other NSAIDs, high blood pressure medication, blood thinners, corticosteroids, methotrexate, cyclosporin, lithium, phenytoin;
- have any other medical problem(s) such as alcohol abuse, bleeding problems, etc.

FLOCTAFENINE should not be used by children, except as recommended by a doctor.

Long-term use of FLOCTAFENINE is not recommended.

**WHILE TAKING THIS MEDICATION:**

- tell any other doctor, dentist or pharmacist that you consult or see, that you are taking this medication;
- some NSAIDs may cause drowsiness or fatigue in some people taking them. Be cautious about driving or participating in activities that require alertness if you are drowsy, dizzy or lightheaded after taking this medication;
- check with your doctor if you are not getting any relief or if any problems develop;
- report any untoward reactions to your doctor. This is very important as it will aid in the early detection and prevention of potential complications.
- stomach problems may be more likely to occur if you drink alcoholic beverages. Therefore, do not drink alcoholic beverages while taking this medication;
- check with your doctor immediately if you experience unexpected weakness while taking this medication, or if you vomit any blood or have dark or bloody stools;
- some people may become more sensitive to sunlight than they are normally. Exposure to sunlight or sunlamps, even for brief periods of time, may cause sunburn, blisters on the skin, skin rash, redness, itching or discoloration; or vision changes. If you have a reaction from the sun, check with your doctor;
- check with your doctor immediately if chills, fever, muscle aches or pains, or other flu-like symptoms occur, especially if they occur shortly before, or together with, a skin rash. Very rarely, these effects may be the first signs of a serious reaction to this medication;
- YOUR REGULAR MEDICAL CHECKUPS ARE ESSENTIAL.

## SIDE EFFECTS OF THIS MEDICATION

Along with its beneficial effects, FLOCTAFENINE like other NSAID drugs, may cause some undesirable reactions.

Elderly, frail or debilitated patients often seem to experience more frequent or more severe side effects.

Although not all of these side effects are common, when they do occur they may require medical attention.

### CHECK WITH YOUR DOCTOR IMMEDIATELY IF ANY OF THE FOLLOWING ARE NOTED:

- bloody or black tarry stools;
- rapid heartbeat;
- shortness of breath, wheezing, any trouble in breathing, or tightness in the chest;
- skin rash, hives or swelling, itching;
- abnormalities of taste, dry mouth;
- vomiting or persistent indigestion, nausea, stomach pain, stomach cramps, gas, constipation or diarrhea;
- yellow discoloration of the skin or eyes;
- any change in the amount of or colour of your urine (dark red or brown);

- any pain or difficulty experienced while urinating, and/or strong smelling urine;
- headache;
- insomnia;
- swelling of the feet or lower legs;
- malaise, fatigue, drowsiness, loss of appetite;
- blurred vision or any visual disturbance;
- mental confusion, depression, dizziness, lightheadedness;
- nervousness, irritability;
- hearing problems (ringing in your ears);
- abnormal liver function.

Other side effects not listed above may also occur in some patients. If you notice any other effects, check with your doctor.

### DOSING

The usual adult dose of FLOCTAFENINE is one 200 or 400 mg tablet every 6 to 8 hours as required. You should not take more than 1200 mg in a day unless directed by your doctor or dentist. The tablets should be taken after a meal or food, with a glass of water.

## STORAGE

FLOCTAFENINE tablets should be stored at room temperature (15 to 30°C) and protected from light.

FLOCTAFENINE IS NOT RECOMMENDED FOR USE IN CHILDREN SINCE SAFETY AND EFFECTIVENESS HAVE NOT BEEN ESTABLISHED.

DO NOT KEEP OUTDATED MEDICINE OR MEDICINE NO LONGER NEEDED.

KEEP OUT OF THE REACH OF CHILDREN.

THIS MEDICATION HAS BEEN PRESCRIBED FOR YOUR MEDICAL PROBLEM. DO NOT GIVE IT TO ANYONE ELSE.

IF YOU REQUIRE MORE INFORMATION ON THIS DRUG, CONSULT YOUR DOCTOR OR PHARMACIST.

## PHARMACOLOGY

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<sub>50</sub>'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 10-20 mg/kg of floctafenine were comparable to doses of 2-10 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 Freund's adjuvant. The ED<sub>50</sub>'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<sub>2</sub>, 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-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.

Pharmacokinetics: The pharmacokinetics and metabolism of <sup>14</sup>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. Only negligible quantities cross the blood-brain barrier, indicating that the analgesic activity is exclusively peripheral.

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.

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.

## **TOXICOLOGY**

Floctafenine was investigated for acute toxicity orally in mouse, rat and rabbit: respective LD<sub>50</sub> values were 2.83 g/kg, 1.03 g/kg and 700 mg/kg. Intravenous and intraperitoneal LD<sub>50</sub> 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.

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.

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 4-18, 1-26 and 4-41 :g/mL for the low, intermediate and high dosage groups respectively, and falling to approximately 4 :g/mL after 24 hours.

## REPRODUCTION

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.

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