



SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ZERO-P 100 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Active substance:

Flurbiprofen.....100 mg

Excipients with known effect:

Lactose monohydrate (from cow's milk).....100 mg

Lactose monohydrate (from bovine milk).....4.8 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Blue-colored, oblong tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

It is indicated for the treatment of the signs and symptoms of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis, as well as for the treatment of acute musculoskeletal pain, acute gout arthritis and dysmenorrhea.

4.2 Posology and method of administration

Posology/frequency and duration of administration

As with other non-steroid anti-inflammatory drugs (NSAIDs), undesirable effects may be minimized by using the lowest effective dose. After observing the response to initial therapy with ZERO-P, the dose and frequency should be adjusted to suit an individual patient's needs.

The recommended daily dose is 200 mg in divided doses. The total daily dosage may be increased to 300 mg depending upon the severity of the symptoms.

For relief of the symptoms of rheumatoid arthritis and osteoarthritis, the recommended ZERO-P dose is 200 to 300 mg per day, divided for administration 2 or 3 times a day.

For menstrual pain, a dosage of 100 mg may be administered at the start of symptoms followed by 100 mg given at 4 to 6 hour intervals. The maximum daily dosage is 300 mg.

The largest recommended single dose in a multiple-dose daily regimen is 100 mg.

It should be taken right after a meal with a sufficient amount of water (e.g. a glass of water).

Additional information on special populations

Pediatric population

There is no data on its administration for children.

Geriatric population

Caution should be exercised for the patients aged over 65. As with any NSAID, elderly patients may have a higher incidence of gastrointestinal complaints than younger patients, including ulceration, bleeding, flatulence, and abdominal pain.



Hepatic impairment

A patient with symptoms and/or signs suggesting liver dysfunction, or with abnormal liver test values, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with ZERO-P (see section 4.4 - Hepatic effects). It should not be administered for the patients with severe hepatic impairment (see section 4.3).

Renal impairment

Dose reduction may be necessary in patients with significant decrease of renal function to prevent accumulation of flurbiprofen metabolites. These patients should be monitored closely (see section 4.4 - Renal effects). It should not be administered for the patients with severe renal impairment (see section 4.3).

4.3 Contraindications

- ZERO-P is contraindicated in patients with known hypersensitivity to flurbiprofen. ZERO-P should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see section 4.4 - Anaphylactic reactions and Pre-existing asthma). ZERO-P should not be given to patients with aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs.
- It is contraindicated in patients with active, or history of, peptic ulcer.
- It is contraindicated in patients with a history of gastrointestinal bleeding or perforation associated with previous NSAID therapy.
- It is contraindicated in gastrointestinal or cerebrovascular bleeding, and other bleedings.
- It is contraindicated in patients with severe heart failure, hepatic failure and renal failure.
- Its administration as painkiller is contraindicated before and after surgery for patients who had coronary artery by-pass graft operation.
- It is contraindicated during the last trimester of pregnancy.

4.4 Special warnings and precautions for use

Concomitant use of ZERO-P with NSAIDs other than aspirin, including COX-2 inhibitors, should be avoided. Concomitant use of systemic NSAIDs and other NSAIDs may cause an increase in the frequency of gastrointestinal (GI) ulcers and bleeding.

Cardiovascular Risk

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.
- ZERO-P is contraindicated for treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery as painkiller.

Gastrointestinal Risk

- NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during treatment and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.



Warnings

Cardiovascular thrombotic effects

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to 3 years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. Patients with known or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with flurbiprofen, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur (see section 4.3).

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID increase the risk of serious GI events (see section 4.4 Gastrointestinal (GI) effects - GI ulceration, bleeding and perforation risk).

Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke (see section 4.3).

Hypertension

NSAIDs including flurbiprofen, can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including flurbiprofen, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

Congestive cardiac impairment and edema

Like other drugs known for inhibiting prostaglandin synthesis, fluid retention and edema have been observed in some patients taking NSAIDs including flurbiprofen. Therefore, ZERO-P should be used with caution in patients with fluid retention or heart impairment.

Gastrointestinal (GI) effects - GI ulceration, bleeding and perforation risk

NSAIDs can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Minor upper GI problems, such as dyspepsia, are common, usually developing anytime in therapy. Therefore, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs, even in the absence of previous GI tract symptoms. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Most patients who develop a serious upper GI adverse event on NSAID therapy have no symptoms. Upper GI ulcers, gross bleeding or perforation, caused by NSAID, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue, thus increasing the likelihood of developing a serious GI event at some time during the course of therapy. Even short-term therapy has its risks.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding.



Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population. **To minimize the potential risk for an adverse GI event in patients treated with an NSAID, 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.

Studies have shown that patients with a prior history of peptic ulcer disease and/or GI bleeding and who use NSAIDs, have a greater than 10-fold higher risk for developing a GI bleed than patients with neither of these risk factors. Additional history of ulcer pharmaco-epidemiological studies have identified co-therapies or comorbid conditions that may increase the risk for GI bleeding such as: use of aspirin, treatment with oral corticosteroids, treatment with anticoagulants or selective serotonin reuptake inhibitors, prolonged treatment with NSAIDs, smoking, alcohol dependence, advanced age and poor general health status.

Renal effects

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

In clinical studies, the elimination half-life of flurbiprofen was unchanged in patients with renal impairment. Flurbiprofen metabolites are eliminated primarily by the kidneys. Elimination of 4'-hydroxy-flurbiprofen was reduced in patients with moderate to severe renal impairment. Therefore, decrease in dose may be needed in patients with significant lowering of the renal functioning to inhibit accumulation of flurbiprofen metabolites. These patients should be monitored closely.

Advanced renal disease

Treatment with flurbiprofen is not recommended in these patients with advanced renal disease. If flurbiprofen therapy must be initiated, close monitoring of the patients renal function is advisable (see section 4.4-Renal effects).

Anaphylactoid Reactions

As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to flurbiprofen. Flurbiprofen should not be given to patients with the aspirin-triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs. In post-marketing experience, rare cases of anaphylactic/anaphylactoid reactions and angioedema have been reported in patients receiving flurbiprofen (see section 4.3, Special warnings and precautions for use- Pre-existing asthma). Immediate intervention should be exercised in case of an anaphylactic reaction.

Dermatological effects

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported very rarely in association with



the use of NSAIDs, including flurbiprofen. These serious events can occur without any symptoms. Patients should be informed about signs and symptoms of serious skin reactions and flurbiprofen should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Precautions

Hepatic effects

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, including flurbiprofen. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice, fulminant hepatitis, liver necrosis, and hepatic impairment, some of them with fatal outcomes have been reported.

A patient with symptoms and/or signs suggesting liver dysfunction, or with abnormal liver test values, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with ZERO-P. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), ZERO-P should be discontinued.

Hematological effects

Anemia is sometimes seen in patients receiving NSAIDs, including flurbiprofen. 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 ZERO-P, should have their hemoglobin or hematocrit checked periodically even if they do not exhibit any signs or symptoms of anemia.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Flurbiprofen does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT). Patients receiving ZERO-P who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Pre-existing asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, ZERO-P should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma (see section 4.3).

Changes in vision

Blurred and/or diminished vision has been reported with the use of flurbiprofen and other NSAIDs. Patients experiencing eye complaints should have ophthalmologic examinations.

Systemic lupus erythematosus (SLE) and other connective tissue diseases

In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis.



Laboratory tests

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs of symptoms of GI bleeding. Patients on long-term treatment with NSAIDs should have their CBC and chemistry profile checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (e.g. eosinophilia, rash etc.), or abnormal liver tests persist or worsen, flurbiprofen should be discontinued.

Impaired female fertility

Flurbiprofen can impair female fertility. Therefore, it is not recommended for women attempting to conceive.

Concomitant use with oral anticoagulants

Concomitant use of NSAIDs, including flurbiprofen, and oral anticoagulants should be administered with caution as they increase the risk of GI or non-GI bleeding. Oral anticoagulants include the warfarin/coumarin-type and newly developed oral anticoagulants (e.g., apixaban, dabigatran, rivaroxaban). Anticoagulant/INR should be monitored in patients using warfarin/coumarin-type anticoagulants (see section 4.5).

Additional information on special populations

Pediatric population

There is no data on its use in children.

Geriatric population

As with any NSAID, caution should be exercised in treating the elderly (65 years and older). Clinical experience with flurbiprofen suggests that elderly patients may have a higher incidence of gastrointestinal complaints than younger patients have, including ulceration, bleeding, flatulence, bloating, and abdominal pain. To minimize the potential risk for gastrointestinal events, the lowest effective dose should be used for the shortest possible duration (see section 4.4 - Gastrointestinal (GI) effects - GI ulceration, bleeding and perforation risk). Likewise, elderly patients are at greater risk of developing renal decompensation (see section 4.4 - Renal Effects).

Excipients

ZERO-P contains 104.8 mg lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB)

Reports suggest that NSAIDs may diminish the effectiveness of diuretics and other antihypertensive drugs including ACE-inhibitors, ARBs, and beta-blockers. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function), the co-administration of an ACE inhibitor or ARB cyclooxygenase inhibitor may result in further deterioration of renal function, including possible acute renal impairment, which is usually reversible. These interactions should be considered in patients taking flurbiprofen concomitantly with ACE inhibitors or ARBs and/or diuretics.



Therefore, the combination should be administered with caution, especially in the elderly.

Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

Anticoagulants: The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone. The physician should be cautious when administering ZERO-P to patients taking warfarin or other anticoagulants.

Aspirin: Concurrent administration of aspirin lowers serum flurbiprofen concentrations. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of ZERO-P and aspirin is not generally recommended because of the potential for increased adverse effects.

Beta-adrenergic blocker agents: Flurbiprofen attenuated the hypotensive effect of propranolol but not atenolol. The mechanism underlying this interference is unknown. Patients taking both flurbiprofen and a beta-blocker should be monitored to ensure that a satisfactory hypotensive effect is achieved.

Diuretics: NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with ZERO-P, the patient should be observed closely for signs of renal impairment (see section 4.4- Renal Effects), as well as diuretic efficacy.

Lithium: NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by around 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Methotrexate: NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Especially in patients taking high doses of methotrexate, caution should be exercised when NSAIDs and methotrexate are administered together, as the use of NSAIDs may lead to an increase in the plasma level of methotrexate.

Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding.

Antiplatelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding.

Cimetidine, Ranitidine: A small but statistically significant increase in flurbiprofen serum concentration may result with administration of these agents.

Digoxin: Concurrent administration with flurbiprofen did not reveal a change in steady state serum levels of either drug. However, NSAIDs may exacerbate cardiac impairment, reduce GFR (glomerular filtration rate) and increase plasma glycoside levels.



Oral hypoglycemic agents: Although there was a slight reduction in blood sugar concentrations during concomitant administration of flurbiprofen and hypoglycemic agents, there were no signs or symptoms of hypoglycemia.

Quinolone antibiotics group: NSAIDs can increase the risk of convulsions associated with quinolone antibiotics.

Caution should be used when NSAIDs are administered concomitantly with zidovudine, ticlopidine, tacrolimus and cyclosporine.

Tacrolimus: Concomitant administration of tacrolimus and any NSAID may increase the nephrotoxic effect.

Cyclosporine: Like flurbiprofen, COX inhibitors increase risk of nephrotoxicity due to their effects on renal prostaglandin.

Additional information on special populations

Pediatric population

No data is available.

Geriatric population

Antacids: When used in geriatric subjects, antacid suspensions caused a reduction in the rate but not the extent of flurbiprofen absorption.

4.6 Fertility, pregnancy and lactation

General recommendation

The pregnancy category is “C” for the 1st and 2nd trimesters but it is “D” for the 3rd trimester.

Women of childbearing potential/Contraception

No data is available.

Pregnancy

Reproductive studies conducted in rats and rabbits showed no evidence of developmental abnormalities. However, animal studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women. ZERO-P should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Inhibition of prostaglandin synthesis may adversely affect the pregnancy. Data from epidemiological studies suggest an increased risk of spontaneous miscarriage 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.

Because of the known effects of NSAIDs on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy (third trimester of pregnancy) should be avoided.

Breast-feeding

Concentrations of flurbiprofen in breast milk and plasma of nursing mothers suggest that a nursing infant could receive approximately 0.1 mg flurbiprofen per day in the established



milk of a woman taking flurbiprofen 200 mg/day. Because of possible adverse effects of prostaglandin-inhibiting drugs on neonates, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the benefit of the drug to the mother.

Fertility

In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. Effects of flurbiprofen on labor and delivery in pregnant women are unknown.

Due to its mechanism of action, administration of NSAIDs for some women may delay or inhibit ovarian follicular rupture associated with reversible infertility. Termination of the administration of NSAIDs, including flurbiprofen, should be taken into consideration for women who are having problems of conceiving or who are subject to studies due to infertility.

4.7 Effects on ability to drive and use machines

Undesirable effects such as tiredness, drowsiness, anxiety and visual disturbances are possible after taking NSAIDs. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

Undesirable effects are classified using following system: very common ($\geq 1/10$), common ($\geq 1/100$ and $< 1/10$), uncommon ($\geq 1/1,000$ and $< 1/100$), rare ($\geq 1/10,000$ and $< 1/1,000$) and very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Reported adverse events in patients receiving ZERO-P or other NSAIDs:

	Common	Uncommon	Rare	Not known
Infections and infestations	Rhinitis, signs and symptoms of and urinary tract infection			
Blood and lymphatic system disorders		Iron deficiency anemia		Inhibition of platelet aggregation
Immune system disorders			Anaphylactic reactions	
Metabolism and nutrition disorders	Body weight changes	Hyperuricemia, fluid retention		
Psychiatric disorders	Anxiety, depression, insomnia, nervousness	Confusion		
Nervous system disorders	Amnesia, dizziness, headache, increased reflexes, somnolence, tremor	Ataxia, cerebrovascular ischemia, paresthesia, parosmia,		
Eye disorders	Changes in vision	Conjunctivitis		
Ear and labyrinth disorders	Tinnitus			
Cardiac		Heart failure	Myocardial	



disorders			infarction	
Vascular disorders		Vascular diseases, vasodilatation, hypertension		
Respiratory, thoracic and mediastinal disorders		Asthma, epistaxis		
Gastrointestinal disorders	Abdominal pain, constipation, diarrhea, dyspepsia, flatulence, GI bleeding, nausea, vomiting	Bloody diarrhea, esophageal disease, gastritis, hematemesis, peptic ulcer disease, stomatitis, GI ulcer	GI perforation	
Hepatobiliary disorders		Hepatitis		
Skin and subcutaneous tissue disorders	Rash	Angioedema, eczema, pruritus, urticaria		
Musculoskeletal and connective tissue and bone disorders		Twitching		
Renal and urinary disorders		Hematuria, renal failure	Glomerulonephritis, renal papillary necrosis, nephrotic syndrome	
General disorders	Asthenia, edema, malaise	Chills, fever		
Investigations	Elevated hepatic enzymes	Decrease in hemoglobin and hematocrit		

The following adverse effects are obtained principally from worldwide post-marketing surveillance and literature. It is not always possible to reliably estimate their frequency.

	Adverse effects
Blood and lymphatic system disorders	Aplastic anemia, hemolytic anemia, thrombocytopenia
Immune system disorders	Anaphylaxis
Gastrointestinal disorders	Colitis, exacerbation of inflammatory bowel disease, small intestine inflammation with loss of blood and protein
Hepatobiliary disorders	Cholestatic and non-cholestatic jaundice
Skin and subcutaneous tissue disorders	Exfoliative dermatitis, photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrosis
Nervous system disorders	Aseptic meningitis
Renal and urinary	Interstitial nephritis



disorders	
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Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

Symptoms following acute overdoses with NSAIDs are usually limited to lethargy, drowsiness, nausea, vomiting, altered mental status, diminished muscle tone, headache, diplopia, elevated liver enzymes, respiratory depression, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding may occur. Hypertension, acute renal failure, respiratory depression and coma may also occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, which may also occur following an overdose.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Non-selective COX inhibitors

ATC code: M01AE09

ZERO-P contains flurbiprofen, a non-steroidal anti-inflammatory drug that exhibits antiinflammatory, analgesic, and antipyretic activities. The mechanism of action of flurbiprofen, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition.

5.2. Pharmacokinetic properties

General properties

Absorption

The mean oral bioavailability of flurbiprofen from flurbiprofen tablets 100 mg is 96% compared to oral solution. Flurbiprofen is rapidly and non-stereoselectively absorbed from flurbiprofen tablets, with peak plasma concentrations occurring at about 2 hours. Administration of flurbiprofen tablets with either food or antacids may alter the rate but not the extent of flurbiprofen absorption. Ranitidine has been shown to have no effect on either the rate or extent of flurbiprofen absorption.

Distribution

The apparent volume of distribution (V_z/F) of both R- and S-flurbiprofen is approximately 0.12 L/Kg. Both flurbiprofen enantiomers are more than 99% bound to plasma proteins, primarily albumin. Plasma protein binding is relatively constant for the typical average



steady-state concentrations (≤ 10 mcg/ml) achieved with recommended doses.

Biotransformation

Several flurbiprofen metabolites have been identified in human plasma and urine. These metabolites include 4'-hydroxy-flurbiprofen, 3',4'-dihydroxy-flurbiprofen, 3'-hydroxy-4'-methoxy-flurbiprofen, their conjugates, and conjugated flurbiprofen. Unlike other aryl propionic acid derivatives (eg, ibuprofen), metabolism of R-flurbiprofen to S-flurbiprofen is minimal. *In vitro* studies have demonstrated that cytochrome P450 2C9 plays an important role in the metabolism of flurbiprofen to its major metabolite, 4'-hydroxy-flurbiprofen. The 4'-hydroxy-flurbiprofen metabolite showed little anti-inflammatory activity in animal models of inflammation. Flurbiprofen does not induce enzymes that alter its metabolism. The total plasma clearance of unbound flurbiprofen is not stereoselective, and clearance of flurbiprofen is independent of dose when used within the therapeutic range.

Flurbiprofen metabolism is predominantly mediated via cytochrome P450 CYP 2C9 in the liver. Flurbiprofen should be administered with caution for patients with known slow cytochrome P450 2C9 or patients who are thought to be so in align with their pre existing exposure to other cytochrome P450 2C9 substrates. It is because that these patients may have abnormal plasma level due to their low metabolic clearance.

Elimination

Following dosing with flurbiprofen, less than 3% of flurbiprofen is excreted unchanged in the urine, with about 70% of the dose eliminated in the urine as parent drug and metabolites. Because renal elimination is a significant pathway of elimination of flurbiprofen metabolites, dosing adjustment in patients with moderate or severe renal dysfunction may be necessary to avoid accumulation of flurbiprofen metabolites. The mean terminal disposition half-lives ($t_{1/2}$) of R- and S-flurbiprofen are similar, about 4.7 and 5.7 hours, respectively. There is little accumulation of flurbiprofen following multiple doses.

Linearity/Non-linearity

Dose proportionality has not been evaluated.

Characteristics in patients

Hepatic impairment

Hepatic metabolism may account for >90% of flurbiprofen elimination, so patients with hepatic disease may require reduced doses of ZERO-P compared to patients with normal hepatic function. The pharmacokinetics of R- and S-flurbiprofen were similar, however, in alcoholic cirrhosis patients (N=8) and young healthy volunteers (N=8) following administration of a single 200 mg dose of flurbiprofen tablets.

Flurbiprofen plasma protein binding may be decreased in patients with liver disease and serum albumin concentrations below 3.1 g/dl.

Renal impairment

Renal clearance is an important route of elimination for flurbiprofen metabolites, but a minor route of elimination for unchanged flurbiprofen ($\leq 3\%$ of total clearance). The unbound clearances of R- and S-flurbiprofen did not differ significantly between normal healthy volunteers (N=6, 50 mg single dose) and patients with renal impairment (N=8, insulin clearances ranging from 11 to 43 ml/min, 50 mg multiple doses). Flurbiprofen plasma protein binding may be decreased in patients with renal impairment and serum albumin concentrations below 3.9 g/dl. Elimination of flurbiprofen metabolites may be reduced in patients with renal impairment.



Flurbiprofen is not significantly removed from the blood into dialysate in patients undergoing continuous ambulatory peritoneal dialysis.

Pediatric population

Pharmacokinetics of flurbiprofen has not been studied in pediatric patients.

Geriatric population

Flurbiprofen pharmacokinetics was similar in geriatric arthritis patients, younger arthritis patients, and young healthy volunteers receiving flurbiprofen 100 mg tablets as either single or multiple doses.

5.3. Preclinical safety data

Carcinogenicity, reproductive and teratology studies were conducted. Even though flurbiprofen was not found to have carcinogenic, teratogenic or adverse reproductive effects in preclinical studies, see section 4.6 for its effects on fertility.

6. PHARMACEUTICAL PROPERTIES

6.1 List of excipients

Lactose monohydrate (from cow's milk)
Magnesium stearate
Microcrystalline cellulose pH 101
Microcrystalline cellulose pH 102
Colloidal silicon dioxide
Croscarmellose sodium
Hydroxy propyl methyl cellulose
Film coating agent: Opadry II blue 32K20439
Lactose monohydrate (from bovine milk)
Hydroxy propyl methyl cellulose
Titanium dioxide
Triacetin
FD&C blue #2 indigo carmine aluminum lake
Yellow iron oxide

6.2 Incompatibilities

There are no known incompatibilities.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at room temperature below 25°C.

6.5 Nature and contents of container

Blisters containing 5 film-coated tablets, consisting of transparent PVC/PVDC on one side and printed aluminum foil on the other side.

Each cardboard box contains 15 or 30 film-coated tablets.

*Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling



Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.

Halkalı Merkez Mah. Basın Ekspres Cad. No:1

34303 Küçükçekmece – İSTANBUL / TÜRKİYE

8. MARKETING AUTHORIZATION NUMBER

220/98

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

Date of first authorization : 16.10.2009

Date of last renewal :

10. DATE OF REVISION OF THE TEXT