8028755-9093

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

TORVIN

(Flupirtine Maleate Capsules)

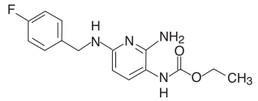
COMPOSITION

Each capsule contains :
Flupirtine Maleate 100 mg
Approved colours used in capsule shell

DESCRIPTION

Flupirtine maleate is a nonopioid centrally-acting analgesic agent, structurally dissimilar from other analgesics. It is a pyridine derivative with the chemical name of ethyl-2-amino 6-(4-fluorobenzylamino) 3-pyridylcarbamate maleate. Molecular formula: $C_{15}H_{17}FN_4O_2.C_4H_4O_4$ and Molecular weight is 420.4.

It has the following structural formula::



PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: analgesic class is triaminopiridine code ATC N02BG07

Flupirtine is the head of the class of substances defined as SNEPCO (Selective Neuronal Potassium Channel Opener-substances that open on a selective neuronal potassium channels). It 's a non-opioid analgesic that has no central action potential additive or cause any development of tolerance.

Flupirtine activates a G protein-coupled internally to neuronal channels "inward rectifier" K^+. The release of K^+ causes a stabilization of membrane potential, while it reduced the activation of the membranes of nerve cells. This leads to indirect inhibition of activation of NMDA receptors, as blocking of NMDA receptors by Mg^{2+} is removed only

with the depolarization of the cell membrane (indirect antagonism of NMDA receptors).

If used at concentrations therapeutically valid, does not bind to receptors α1, α2, 5HT1, 5HT2, muscarinergic central nicotinergic, dopamine, benzodiazepine, opiates.

This active ingredient that acts at the central level has three main effects: Analgesic effect The selective opening of K^+ channels in neuronal voltage-independent and the subsequent release of K^+ stabilizes the resting potential of nerve cells. Consequently, the neurons become less excitable. The resulting indirect antagonism of the NMDA-Flupirtine protects neurons from the entry of Ca^{2+}. In this case, the sensitizing effect due to the increase of intracellular Ca^{2+} is buffered. So in the case of neuronal stimulation, the transmission of ascending nociceptive impulses will be inhibited. Mio-relaxing effect The pharmacological effects described for the analgesic action are supported at the functional level by stimulation of Ca^{2+} entry into mitochondria, as demonstrated in effective therapeutic concentrations. Mio-relaxing effects are produced by depression of the transmission of depression from which the motor neurons and the consequent effect on interneurons. However, this is not an effect of type-I relaxed in general, but mostly a tension-relaxing effect. Effect on the processes of chronic Processes should be evaluated as chronic conduction processes are caused by neuronal plasticity of neuronal function.

Through the induction of intracellular processes, the plasticity of neuronal function due to a phenomenon called "wind up", resulting in a greater response to the next incoming pulse. NMDA receptors are of particular importance in the development of these changes (gene expression). The indirect block caused by Flupirtine leads to suppression of these changes. This contrasts with the chronic pain clinically reflected and manifested in the case of chronic, stabilization of membrane potential leads to a "cancellation" of the memory of pain and decreased sensitivity to it.

Pharmacokinetic properties

Absorption

The Flupirtine is well tolerated after oral and rectal bioavailability with respectively 90 and 72.5%: plasma half-life is approximately 9 hours and did not observe any significant accumulation after multiple dosing.

Metabolism

About ¾ of the administered Flupirtine are metabolized in the liver. During the metabolic process, the metabolite M1 hydrolysis reaction (Phase I) of the structure and acetylation urethane reaction (Phase II) of this leads to the formation of amino derivative of the metabolite M1 (2-amino-3-acetamino-6- [4-fluoro]-benzilaminopiridina). This metabolite has analgesic power that is approximately one fourth of that of Flupirtine and thus contributes to analgesic action thereof. No further research was conducted to identify which isoenzyme is primarily involved in the (less important) process of oxidative degradation.

Elimination

The main part of the dose (69%) is excreted by the kidneys. This portion is as follows: 27% of unchanged drug, 28% of the M1 metabolite (acetyl metabolite), 12% of the metabolite M2 (hippuric acid beta-fluoro) and the remaining third consists of several secondary metabolites of the structure is still not known. A small part of the dose is excreted through the bile and feces.

In elderly patients, has been an increased half-life after repeated dosing. Plasma levels are proportional to dose.

Preclinical safety data

In the course of toxicological studies conducted on animals using doses pharmacodynamics effective, there has been no toxic effects of flupirtine maleate on organs or systems, or a functional nor a morphological level. At extremely high doses - and in certain cases of acute administration - was observed in the central nervous sedation and potential hepatotoxicity in the sense of increased liver metabolic load.

In animal experiments of acute and sub-chronic relating to interactions with other medications (especially with non-steroidal analgesics), have not been found any indication of an increase or modification of the toxic effect of individual components. This applies substantially to hepatic metabolic load was observed in acute and chronic studies conducted with Flupirtine maleate on two animal species (mouse and rat). The adaptation to this metabolic load was characterized by a smaller increase in liver enzyme activity (which was still included in the physiological range) by an increase in liver weight accompanied by a low enzyme induction and - compared to the control group - by an insignificant increase in the incidence of isolated cell necrosis of hepatocytes, which were often regenerate even after continuous administration of the substance. Depending on the series of experiments, non-toxic doses determined in studies of chronic toxicity and reproductive studies, appear to be equal to three times the maximum recommended daily human therapeutic dose. Test in-vitro and in vivo did not indicate any type of mutagenic effect.

Carcinogenicity studies in mice and rats revealed no carcinogenic potential. In the study of mice, hepatocyte nodular hyperplasia was found, probably due to reactions of adjustment of the load cell metabolism after prolonged administration of high doses of Flupirtine maleate.

In reproductive toxicity studies, neither fertility nor the development of the offspring were affected when the maximum tolerated dose was administered to the animals parents. There were no teratogenic effects at doses up highly toxic.

INDICATIONS

Flupirtine is indicated for the treatment of acute and chronic pain, i.e, for painful increased muscle tone of the posture and motor muscles, primary headache, tumor pain, dysmenorrhea and pain after traumatologic/orthopedic and injuries.

CONTRAINDICATIONS

Hypersensitivity to the active substance or any excipients
In patients with myasthenia gravis.

WARNINGS AND PRECAUTIONS

Flupirtine should be used with caution in patients with liver disorders and / or alcoholism. Patients with impaired liver or kidney function should be monitored by regular and repeated liver enzymes as well as serum creatinine values: in such cases it is necessary to make an adjustment in dosage and interval between doses. Patients older than 65 years and / or clearly impaired renal function and / or hypoalbuminemia should take Flupirtine only upon prescription: in such cases may need a lower dose extended interval between doses.

Patients with hepatic encephalopathy and should not be used with Flupirtine as the onset or worsening encephalopathy may occure, as well as ataxia and motor disorders.

Treatment with Flupirtine maleate can manifest false positive test for bilirubin, urobilinogen and urine proteins in urinary casts. Similarly, the results of the analytical methods used for the quantitative determination of serum bilirubin may be affected.

In isolated cases, treatment with high doses can lead to a green coloration of urine, however this fact is of no clinical significance.

Keep out of reach of children.

DRUG INTERACTIONS

Flupirtine may increase the effect of alcohol and substances with sedative or muscle relaxant activity. Given the high protein binding of Flupirtine, the displacement from protein binding of other protein-bound drugs administered can be observed. The corresponding tests were conducted in vitro with diazepam, warfarin, acetylsalicylic acid, benzylpenicillin, digitoxin, glibenclamide, propranolol and clonidine. Only in the case of warfarin and diazepam, the displacement from albumin binding reached a level where one can not exclude an increase in the pharmacological action of these products, concomitant administration of Flupirtine maleate. In patients treated concurrently with Flupirtine and coumarin derivatives, it is therefore recommended to make the test more often so quick to highlight the possible effects or to reduce the dose of coumarin administered if required. In the case of other anticoagulant agents (eg, SSA and others), no further information available
about possible interactions.

Flupirtine When used in combination with other medicines which are also mainly metabolized in the liver, should be monitored for the liver enzymes at the beginning of treatment and at regular intervals thereafter. Association of Flupirtine maleate with drugs containing paracetamol and / or carbamazepine should be avoided.

ADVERSE EFFECTS

Very common (> 1 / 10): fatigue (about 15% of patients), particularly at the beginning of therapy. Common (> 1 / 100, <1 / 10): dizziness, heartburn, nausea / vomiting, stomach upset, constipation, sleep disturbances, sweating, lack of appetite, depression, tremor, headache, abdominal pain, dry mouth, restlessness / nervousness, flatulence, diarrhea. Uncommon (> 1 / 1000, <1 / 100): disorientation, visual disturbances and allergic reactions.

Allergic reactions can manifest as rash, hives and itching in isolated cases accompanied by an increase in body temperature.

Very rare (<1 / 10000): data that reflect the experience of the practical use very rare reports of isolated or side effects affecting the liver: Transaminases increased (in most cases, this effect is reversible after dose reduction and / or discontinuation of Flupirtine maleate), drug-induced hepatitis (acute or chronic, or non-jaundiced jaundiced, with or without cholestatic elements). In individual cases with clinical symptoms, the liver was already damaged before or after co-administration of drugs that affect liver function. Generally, side effects are dose-related. In most cases, they disappear in the course of treatment or prove to be reversible.

DOSE AND METHOD OF ADMINISTRATION

Adults: The average recommended dose is 300-400 mg / day (1 capsule 100 mg repeated every 6-8 hours). The dose is still appropriate to the individual needs, in the opinion of the doctor, up to a maximum of 600 mg / day (200 mg every 8 hours). The maximum dose (600 mg / day) should be used only under medical supervision. Patients aged 65 years or older should begin therapy with a Flupirtine capsule in the morning and evening. The dose may be increased, depending on the intensity of pain and depending on tolerability. In patients with severe renal impairment or hypoalbuminemia, daily dose must not exceed the dose of 300 mg Flupirtine maleate. Higher dose requires close medical supervision of these patients.

Method of administration: The capsules should be swallowed with liquid without chewing. In exceptional cases, the capsules can be opened and can only be given to their content (eg via a cannula). In the case of oral administration of capsule contents, due to the extremely bitter taste, it is recommended to neutralize the taste with appropriate foods (eg banana).

Duration of treatment: Flupirtine is taken to obtain the attenuation or disappearance of pain but should not exceed 4 weeks continuous use. If it is necessary to prolonged treatment, medical monitoring of liver function (ALT) should be implemented.

Pregnancy and Lactation

Flupirtine should not be used during pregnancy.
Should flupirtine must necessarily be given to lactating women, breast-feeding should be stopped.

OVERDOSAGE

Isolated reports of attempting suicide have been reported after intentional overdose, where the consumption of more than 5 g Flupirtine maleate showed the following symptoms: nausea, fatigue, ventricular tachycardia, crying spells, dizziness, disorientation, dry mouth. The normal function is restored within 6-12 hours, or after forced vomiting or with diuresis, activated carbon and electrolyte infusion. Life-threatening symptoms were not observed. The available results from experiments on animals have shown that, in case of overdose or poisoning, the central nervous symptoms and potential hepatotoxicity occurring with an increase in the metabolic stress of the liver are expected. Treatment should be symptomatic. There is no known specific antidote.

EXPIRY

Do not use later than date of expiry.

STORAGE

Store below 25^{O}C, Protected from light and moisture.

PRESENTATION

Torvin is available as blister strips of 10 capsules.

torrent

Marketed by :
TORRENT PHARMACEUTICALS LTD.
Indrad-382 721, Dist. Mehsana, INDIA.

Manufactured by :
LUPIN LTD.
EPIP, SIDCO, Kartholi, Bari Brahmana,
Jammu, J & K - 181133

224792