Gefaget™

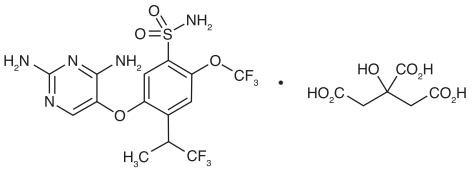
(G e f a p i x a n t)

جیفاگیٹ

Film-coated Tablets 45mg

DESCRIPTION

Gefaget contains Gefapixant Citrate, a selective P2X3 receptor antagonist. Its chemical name is 5-[(2, 4-Diaminopyrimidin-5-yl)oxy]-2-methoxy-4-(propan-2-yl)benzene-1 -sulfonamide monocitrate. Its molecular formula is $C_{14}H_{19}N_5O_4S•C_6H_8O_7$ and the structural formula is:



Gefapixant Citrate

QUALITATIVE AND QUANTITATIVE COMPOSITION

Gefaget (Gefapixant) Tablets are available for oral administration as:

Gefaget Tablets 45mg
Each film-coated tablet contains:
Gefapixant Citrate equivalent to Gefapixant …45mg

CLINICAL PHARMACOLOGY

Mechanism of Action

Gefapixant is a selective antagonist of the P2X3 receptor. Gefapixant also has activity against the P2X2/3 receptor subtype. P2X3 receptors are ATP-gated ion channels found on sensory C fibers of the vagus nerve in the airways. C fibers are activated in response to inflammation or chemical irritants. ATP is released from airway mucosal cells under conditions of inflammation. Binding of extracellular ATP to P2X3 receptors is sensed as a damage signal by C fibers. Activation of C fibers, which is sensed by the patient as an urge to cough, initiates a cough reflex. Blockade of ATP signaling through P2X3 receptors reduces excessive sensory-nerve activation and excessive cough induced by extracellular ATP.

Pharmacokinetics

Absorption

Following oral administration of Gefapixant, the time to achieve peak plasma concentrations (T_{max}) ranged from 1 to 4 hours. Exposure increases are dose proportional following multiple doses up to 300mg twice daily. The fraction absorbed for Gefapixant is at least 78%.

Effect of food

Relative to fasting conditions, oral administration of a single dose of Gefapixant 50mg with a standard high fat and high calorie meal had no effect on the AUC or C_{max} of Gefapixant.

Distribution

The mean steady-state apparent volume of distribution is estimated to be 138L following oral administration of a 45mg dose.
In vitro, Gefapixant exhibits low plasma protein binding (55%) and has a blood-to-plasma ratio of 1.1. Gefapixant has low CNS penetration.

Metabolism

Hepatic metabolism is a minor route of Gefapixant elimination, involving oxidation and glucuronidation. Following oral administration of [^{14}C] Gefapixant, 14% of the administered dose was recovered as metabolites in the urine and feces. Unchanged Gefapixant is the major drug-related component in plasma (87%), and each circulating metabolite accounted for less than 10% of the total radioactivity detected.

Elimination

Renal excretion is the major route of elimination of Gefapixant and involves both passive renal filtration and active transport mechanisms. Gefapixant is recovered in urine as parent (~64%) or metabolites (~12%), and the remainder is recovered in feces as parent (~20%) or metabolites (~2%). Active renal secretion is estimated to account for ≤ 50% of total elimination. In vitro, Gefapixant is a substrate of MATE1, MATE2K, P-gp, and BCRP transporters. Gefapixant has a terminal half-life ($t_{½}$) of 6 – 10 hours.

Special Population

Patients with renal impairment

Mild or moderate renal impairment (eGFR ≥ 30mL/minute/1.73m^2) does not have a clinically meaningful effect on the exposure of Gefapixant.
In patients with refractory or unexplained chronic cough, the mean AUC and C_{max} of Gefapixant were predicted to increase by 89% and 54%, respectively, in patients with severe renal impairment (eGFR < 30mL/minute/1.73m^2) compared to those with normal renal function. To maintain similar systemic exposures to those with normal renal function, dose adjustment is recommended.

THERAPEUTIC INDICATIONS

Gefaget (Gefapixant) is indicated in adults for the treatment of refractory or unexplained chronic cough.

DOSAGE AND ADMINISTRATION

The recommended dose of Gefaget (Gefapixant) is one 45mg tablet taken orally twice daily with or without food.

Missed Dose

Patients should be instructed that if they miss a dose, they should skip the missed dose and go back to the regular schedule. Patients should not double their next dose or take more than the prescribed one.

Special Population

Elderly (≥ 65 years old)

No dose adjustment is required for elderly patients. Gefapixant is known to be substantially excreted by the kidney. Because elderly patients are more likely to have decreased renal function, the risk of adverse reactions to Gefapixant may be greater in these patients. Care should be taken with initial dosing frequency.

Renal impairment

Dose adjustment is required in patients with severe renal impairment (eGFR <30mL/minute/1.73m^2) not requiring dialysis. The dose should be reduced to one 45mg tablet taken once daily.
No dose adjustment is required in patients with mild or moderate renal impairment (eGFR ≥ 30mL/minute/1.73m^2).

Hepatic impairment

Hepatic metabolism is a minor route of elimination of Gefapixant therefore, no dose adjustment is recommended.

ADVERSE REACTIONS

Very common: Dysgeusia, ageusia and hypogeusia.

Common: Upper respiratory tract infection, decreased appetite, taste disorder, dizziness, cough, oropharyngeal pain, nausea, diarrhoea, dry mouth, salivary hypersecretion, abdominal pain upper, dyspepsia, hypoaesthesia oral, paraesthesia oral and insomnia.

Uncommon: Calculus urinary, nephrolithiasis and calculus bladder.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's Pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

CONTRAINDICATIONS
Gefapixant is contraindicated in patients with hypersensitivity to the active substance or to any of the excipient of the product.

PRECAUTIONS
Obstructive sleep apnoea
In patients with moderate to severe obstructive sleep apnoea who were not using positive airway pressure (PAP), Gefapixant 180mg daily at bedtime was associated with a lower mean SaO_2 and a higher mean proportion of time with SaO_2 < 90% across all sleep stages compared to placebo. For patients with OSA, appropriate treatment for OSA should be considered prior to initiating treatment with Gefapixant.

Hypersensitivity
Gefapixant contains a sulphonamide moiety but is considered to be a nonsulphonylarylamine.
Cross-hypersensitivity of Gefapixant with sulphonamide hypersensitivity cannot be excluded. Gefapixant should be used with caution in patients with known hypersensitivity to sulphonamides.

Acute lower respiratory tract infection
Treatment with Gefapixant should be evaluated and individualised in patients who develop an acute lower respiratory tract infection.

Taste-related adverse reactions
Taste-related adverse reactions were very commonly reported in the clinical studies.
In most patients, these adverse reactions resolved soon after discontinuation of Gefapixant (median time 5 days). In a few patients, these reactions persisted for more than a year after discontinuation.

Effects on ability to drive and use machines
Gefapixant has no or negligible influence on the ability to drive and use machines. In individual cases, dizziness may occur following administration of Gefapixant that may influence the ability to drive and use machines.

Pregnancy
There are no data from the use of Gefapixant in pregnant women. As a precautionary measure, it is preferable to avoid the use of Gefapixant during pregnancy and in women of childbearing potential not using contraception.

Nursing Mothers
Available data in animals have shown excretion of Gefapixant in milk. A risk to newborns/infants cannot be excluded.
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Gefapixant therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

DRUG INTERACTIONS
Effects of other medicinal products on the pharmacokinetics of Gefapixant
Hepatic metabolism is a minor pathway for Gefapixant elimination, and the potential for clinically meaningful drug interactions for Gefapixant with co-administration of inhibitors or inducers of cytochrome P450 (CYP) or uridine 5'-diphosphoglucuronic acid glucuronosyl transferase (UGT) enzymes is low.

Concomitant use of a proton pump inhibitor, omeprazole, did not have a clinically meaningful effect on Gefapixant pharmacokinetics.

Based on in vitro studies, Gefapixant is a substrate of efflux transporters multidrug and toxin extrusion 1 (MATE1), MATE2K, P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP). In a Phase 1 clinical study, a single dose of the MATE1/MATE2K inhibitor pyrimethamine increased Gefapixant AUC by 24%, an amount that is not clinically meaningful, and did not affect Gefapixant C_{max}.

Effects of Gefapixant on the pharmacokinetics of other medicinal products
Based on in vitro studies, the potential of Gefapixant to cause CYP inhibition or induction is low, and therefore it is unlikely that Gefapixant would affect the CYP mediated metabolism of other drugs.
Gefapixant is an inhibitor of MATE1, MATE2K, and organic anion-transporting polypeptide 1B1 (OATP1B1) and OATP1B3 in vitro. However, the risk of clinically meaningful drug interactions via inhibition of these transporters is low for Gefapixant administered at 45mg twice daily.

OVERDOSAGE
In case of overdose, monitor the patient for adverse reactions and institute appropriate supportive measures. Gefapixant is partially removed by hemodialysis.

STORAGE
Do not store above 30°C.
Protect from sunlight and moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
Gefaget (Gefapixant) Tablets 45mg are available in blister pack of 30's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:
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