

SUMMARY PRODUCT CHARACTERISTICS

1 NAME OF THE PRODUCT

Kofed Dry Cough Syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each 5ml contains:

Dextromethorphan HBr BP.....7.5mg

3. PHARMACEUTICAL FORM

Syrup

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Kofed Dry Cough Syrup is indicated for the treatment of conditions in which antitussive effects are desired. The preparation is used for the relief of dry and unproductive cough or if the cough is unduly tiring or hazardous.

4.2 Posology and method of administration:

Route of administration: Oral route

Kofed dry cough syrup is administered by oral route ever 4-6 hours at the dosage given below; or as the physician may deem necessary.

Adults: Two (5ml) spoonful 4 times a day.

Children:

2 to 5years: Take one 5ml spoonful three times a day

5 to 12 years: Take one 5ml spoonful and half three times a day

Under 2 years: Not recommended

Do not take more than 4 doses in 24 hours.

Elderly (over 65 years)

As for adults above.

Hepatic impairment

Due to the extensive hepatic metabolism of dextromethorphan, caution should be exercised in the presence of hepatic impairment (see section 5.2).

Do not exceed the stated dose.

Method of administration:

For oral use

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Dextromethorphan should not be given to patients in, or at risk of developing respiratory failure (for example during an acute asthma attack or in patients with Chronic Obstructive Pulmonary Disease).
- Patients taking monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping MAOI treatment (see section 4.5). There is a risk of serotonin syndrome with the concomitant use of a dextromethorphan and MAOIs and the concomitant use of these medications may cause a rise in blood pressure and/or hypertensive crisis (see section 4.5).
- Patient taking serotonin reuptake inhibitors (SSRIs, see section 4.5) or medications for depression, psychiatric, or emotional conditions or Parkinson's disease.
- Dextromethorphan, should not be given to patients in, or at risk of developing respiratory failure.
- Not to be used in children under the age of 12 years.

4.4 Special warnings and precautions for use

Patients with the following conditions should not use this product, unless directed by a physician: acute or chronic asthma, a persistent or chronic cough such as occurs with chronic bronchitis or emphysema, or where cough is accompanied by excessive secretions.

Causes of chronic cough should be excluded if symptoms are persistent. Any accompanying symptoms should be actively sought and appropriately investigated/ treated. Stop use and ask your healthcare professional if your cough lasts more than 7 days, comes back or is accompanied by a fever, rash or persistent headache. These could be signs of serious conditions.

There have been no specific studies of Dextromethorphan in renal or hepatic dysfunction. Due to the extensive hepatic metabolism of dextromethorphan, caution should be exercised in the presence of hepatic impairment.

Cases of dextromethorphan abuse and dependence have been reported. Caution is particularly recommended for adolescents and young adults as well as in patients with a history of drug abuse or psychoactive substances.

Dextromethorphan is metabolised by hepatic cytochrome P450 2D6. The activity of this enzyme is genetically determined. About 10% of the general population are poor metabolisers of CYP2D6. Poor metabolisers and patients with concomitant use of CYP2D6 inhibitors may experience exaggerated and/or prolonged effects of dextromethorphan. Caution should therefore be

exercised in patients who are slow metabolizers of CYP2D6 or use CYP2D6 inhibitors (see also section 4.5).

This product should be used with caution in atopic children due to histamine release.

This product should not be taken with any other cough and cold medicine.

Use of dextromethorphan with alcohol or other CNS depressants may increase the effects on the CNS and cause toxicity in relatively smaller doses. While taking this product, patients should be advised to avoid alcoholic drinks and consult a healthcare professional prior to taking with central nervous system depressants.

Drug dependence, tolerance and potential for abuse

For all patients, prolonged use of dextromethorphan may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).

Drug withdrawal syndrome

The drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

Serotonin Syndrome

Serotonergic effects, including the development of a potentially life-threatening serotonin syndrome, have been reported for dextromethorphan with concomitant administration of serotonergic agents, such as selective serotonin re-uptake inhibitors (SSRIs), drugs which impair metabolism of serotonin (including monoamine oxidase inhibitors (MAOIs)) and CYP2D6 inhibitors.

Serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, treatment with LemoCalm[®] Dry Cough should be discontinued.

Excipient warnings:

LemoCalm[®] Dry Cough contains Liquid Maltitol Patients with rare hereditary problems of fructose intolerance should not take this medicine.

This product contains Naphthol red (E123), which may cause allergic reactions.

This medicine contains 129.5 mg propylene glycol in each 5 mL

Sodium benzoate: This medicine contains 5 mg in each 5 ml which is equivalent to 1mg/ml.

Sodium: This medicine contains less than 1 mmol sodium (23 mg) per 5 ml, that is

to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Monoamine Oxidase Inhibitors (MAOIs)

Dextromethorphan should not be used concurrently in patients taking monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping treatment with MAOIs as there is a risk of serotonin syndrome (pyrexia, hallucinations, gross excitation or coma, hypertension, arrhythmias).

Do not use if you are now taking a prescription monoamine oxidase inhibitor (MAOI), a selective serotonin reuptake inhibitor (SSRI), or other medications for depression, psychiatric, or emotional conditions, or Parkinson's disease, or for 2 weeks after stopping the medication. If you are not sure if your prescription medication contains one of these drugs, ask a doctor or pharmacist before taking this product.

Quinidine can increase serum concentrations of dextromethorphan markedly and some patients have experienced symptoms of dextromethorphan toxicity when the two agents have been used together.

Amiodarone appears to be able to increase serum concentrations of dextromethorphan.

CNS depressants

Dextromethorphan might exhibit additive CNS depressant effects when co-administered with alcohol, antihistamines, psychotropics and other CNS depressant drugs.

CYP2D6 inhibitors

Dextromethorphan is metabolized by CYP2D6 and has an extensive first-pass metabolism. Concomitant use of potent CYP2D6 enzyme inhibitors can increase the dextromethorphan concentrations in the body to levels multifold higher than normal. This increases the patient's risk for toxic effects of dextromethorphan (agitation, confusion, tremor, insomnia, diarrhoea and respiratory depression) and development of serotonin syndrome. Potent CYP2D6 enzyme inhibitors include fluoxetine, paroxetine, quinidine and terbinafine. In concomitant use with quinidine, plasma concentrations of dextromethorphan have increased up to 20-fold, which has increased the CNS adverse effects of the agent. Amiodarone, flecainide and propafenone, sertraline, bupropion, methadone, cinacalcet, haloperidol, perphenazine and thioridazine also have similar effects on the metabolism of dextromethorphan. If concomitant use of CYP2D6 inhibitors and dextromethorphan is necessary, the patient should be monitored and the dextromethorphan dose may need to

be reduced.

4.6 Fertility, pregnancy and lactation

Although dextromethorphan has been in widespread use for many years without apparent ill consequence, there are no specific data on its use during pregnancy. Caution should therefore be exercised by balancing the potential benefit of treatment against any possible hazards. It is not known whether dextromethorphan or its metabolites are excreted in human milk.

Dextromethorphan should therefore only be used when the potential benefit of treatment to the mother exceeds any possible hazards to the developing foetus or suckling infant.

4.7 Effects on ability to drive and use machines

LemoCalm Dry Cough may cause drowsiness and dizziness. Patients affected should not drive or operate machinery.

LemoCalm Dry Cough can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
 - The medicine has been prescribed to treat a medical or dental problem and
 - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
 - It was not affecting your ability to drive safely

Details regarding a new driving offence concerning driving after drugs have been taken in the UK may be found here: <https://www.gov.uk/drug-driving-law>

4.8 Undesirable effects

Adverse drug reactions (ADRs) identified during clinical trials and post-marketing experience with dextromethorphan are included in the table below by System Organ Class (SOC).

The frequencies are provided according to the following convention:

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 $< 1/1,000$

Very rare <1/10,000, including isolated reports

Not known/Unknown (cannot be estimated from the available data)

ADRs are presented by frequency category based on 1) incidence in adequately designed clinical trials or epidemiology studies, if available, or 2) when incidence cannot be estimated, frequency category is listed as 'Not known'.

Body System (SOC)	Frequency	Adverse Drug Reaction (Preferred Term)
Psychiatric Disorders	Not known Not known Not known Not known	Insomnia Confusional state Drug dependence (see section 4.4) Agitation
Nervous System Disorders	Not known Not known Not known Not known	Seizure Dizziness Psychomotor hyperactivity Somnolence
Respiratory, thoracic and mediastinal Disorders	Not known	Respiratory depression
Gastrointestinal	Not known	Abdominal pain

Disorders	Not known Not known Not known Not known	Diarrhoea Gastrointestinal disorder Nausea Vomiting
Skin and Subcutaneous Tissue Disorders	Not known Not known Not known Not known	Angioedema Pruritus Rash Urticaria
General disorders and administration site conditions	Unknown	Drug withdrawal syndrome

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 Pharmacy and Poisons Reporting System (PvERS) <https://pv.pharmacyboardkenya.org>

4.9 Overdose

Symptoms and signs:

Dextromethorphan is thought to be of low toxicity, but the effects in overdosage will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs.

Dextromethorphan overdose may be associated with nausea, vomiting, dystonia, agitation, stupor, cardiotoxicity (tachycardia, abnormal ECG including QTc prolongation), CNS depression, dizziness, dysarthria (slurred speech), nystagmus, somnolence (drowsiness), hyperexcitability, confusion, toxic psychosis with visual hallucinations, tremor, lethargy, ataxia, serotonin syndrome and mydriasis.

In the event of massive overdose the following symptoms may be observed: coma, respiratory depression, convulsions.

Dextromethorphan overdose is also associated with hallucinations, mixed; psychotic disorders; seizures; clumsiness; dizziness; dysarthria; lethargy; hypertension; serotonin syndrome; tremor; CNS depression; miosis and mydriasis.

Management:

Treatment of overdose should be symptomatic and supportive.

Activated charcoal can be administered to asymptomatic patients who have ingested overdoses of dextromethorphan within the preceding hour.

For patients who have ingested dextromethorphan and are sedated or comatose, naloxone, in the usual doses for treatment of opioid overdose, can be considered. Naloxone has been used successfully to reverse central or peripheral opioid effects of dextromethorphan in children (0.01 mg/kg bodyweight).

Benzodiazepines for seizures and benzodiazepines and external cooling measures for hyperthermia from serotonin syndrome can be used.

5 PHARMACOLOGICAL PROPERTIES

5.3 Pharmacodynamic properties

Pharmacotherapeutic group: Cough suppressant, Opium alkaloids and derivatives

ATC code: R05DA09

Dextromethorphan is the dextrorotatory isomer of 3-methoxy-N-methyl-morphinan. It is a synthetic morphine derivative that, in contrast to its levorotatory isomer, has no significant analgesic, respiratory depressant or physical dependency properties at recommended doses.

Dextromethorphan is a non-opioid antitussive drug. It exerts its antitussive activity by acting on the cough centre in the medulla oblongata, raising the threshold for the cough reflex. The onset of antitussive effects are realised within 15 to 30 minutes of oral administration, lasting for approximately 3 to 6 hours.

The major metabolite of dextromethorphan, dextrorphan, binds with high affinity to σ -receptors to produce its antitussive activity without exhibiting the classic opiate effects that occur from binding into μ - and δ -receptors. Dextrorphan also exhibits binding activity at serotonergic receptors and was shown to enhance serotonin activity by inhibiting the reuptake of serotonin. In larger than therapeutic doses, dextrorphan is also an antagonist of N-methyl-D-aspartate (NMDA) receptors.

5.4 Pharmacokinetic properties

Absorption

Dextromethorphan is rapidly absorbed from the gastrointestinal tract with peak plasma concentrations reached in approximately 2 to 2.5 hours. The low plasma levels of dextromethorphan suggest low oral bioavailability secondary to extensive first-pass (pre-systemic metabolism) in the liver. The maximum clinical effects occur 5 to 6 hours after ingestion of dextromethorphan.

Distribution

Dextromethorphan is widely distributed in the human body.

Dextromethorphan and its active metabolite, dextrorphan, are actively taken up and concentrated in brain tissue. It is not known if dextromethorphan or dextrorphan are excreted in breast milk or cross the placenta.

Biotransformation

Dextromethorphan undergoes rapid and extensive first-pass metabolism in the liver after oral administration. Genetically controlled O-demethylation

(CYP2D6) is the main determinant of dextromethorphan pharmacokinetics in human volunteers.

It appears that there are distinct phenotypes for this oxidation process resulting in highly variable pharmacokinetics between subjects. Unmetabolised dextromethorphan, together with the three demethylated morphinan metabolites dextrorphan (also known as 3-hydroxy-N-methylmorphinan), 3-hydroxymorphinan and 3-methoxymorphinan have been identified as conjugated products in the urine.

Dextrorphan, which also has antitussive action, is the main metabolite. In some individuals metabolism proceeds more slowly and unchanged dextromethorphan predominates in the blood and urine.

As the hepatic metabolism of dextromethorphan is genetically determined, individuals vary in their ability to metabolise dextromethorphan and have been classified as either poor or extensive metabolisers. Dextromethorphan undergoes O-demethylation via CYP2D6 to dextrorphan; N-demethylation to 3-methoxymorphinan via CYP3A4/3A5; which is further metabolised to 3-hydroxy-morphinan via CYP2D6.

Elimination

Dextromethorphan is primarily excreted via the kidney as unchanged parent drug and its active metabolite, dextrorphan. Dextrorphan and 3-hydroxymorphinan are further metabolised by glucuronidation and are eliminated via the kidneys.

The elimination half-life of the parent compound is between 1.4 to 3.9 hours; dextrorphan is between 3.4 to 5.6 hours. The half-life of dextromethorphan in poor metabolisers is extremely prolonged, in the range of 45 hours.

5.5 Preclinical safety data

General toxicology

Acute oral toxicity studies conducted with Dextromethorphan report the following LD₅₀ values (mg/kg): mouse, 210 and rat, 116. Acute subcutaneous toxicity with Dextromethorphan reports the LD₅₀ value (mg/kg): mouse, 112. Acute intravenous toxicity with Dextromethorphan reports the LD₅₀ value (mg/kg): rat, 16.3.

Repeat dose toxicity studies conducted in rats for 13 weeks duration at doses up to 100 mg/kg and 27 weeks at 10 mg/kg, and of 14 weeks in dogs by oral gavage at doses up to 4 mg/kg on five days per week. The only effect recorded was of reduced body weight gain in the rat 13-week study at the highest dose.

Genetic Toxicology

Dextromethorphan hydrobromide was negative in the bacterial reverse mutation assay (Ames test). Dextromethorphan 39 mg/kg is reported to be negative in *in-vivo* mouse micronucleus test and comet assay.

Dextromethorphan was reported to be negative in *in vitro* chromosome aberration assay tested up to 200 µg/ml.

No special requirements

Carcinogenicity

There are no known reports of animal carcinogenicity studies for Dextromethorphan. The overall weight of evidence for Dextromethorphan and its structural analogues, support the conclusion that this class of phenanthrene-based chemicals, and Dextromethorphan, in particular, are not genotoxic in vitro or in vivo

Teratogenicity

There was no association between dextromethorphan and malformations.

Fertility

Mating, gestation, fertility, littering and lactation were studied in rats at doses up to 50 mg/kg and no adverse effects were found.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients

Hydroxyethyl cellulose
Sodium Benzoate
Potassium Sorbate
Propylene Glycol
Sodium Saccharin
Menthol Crystals
Citric Acid
Chocolate Brown Colour
Vanilla Essence Liquid
Purified Water

6.2 Incompatibilities:

None known

6.3 Shelf life:

30 months

6.4 Special precautions for storage:

Store below 30°C

6.5 Nature and contents of the container:

100ml Amber coloured PET bottle

6.6 Special precautions for disposal

None

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11/01/2022

10. DATE OF REVISION OF THE TEXT

11/01/2022