SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT:

KOFDEX® COUGH SYRUP

Strength

Each 5ml contains:

Bromhexine Hydrochloride BP……4mg
Dextromethorphan Hydrobromide BP……5mg
Ammonium Chloride BP ……..50mg

Pharmaceutical/Dosage form

Syrup.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each 5ml contains:

Bromhexine Hydrochloride BP……4mg
Dextromethorphan Hydrobromide BP……5mg
Ammonium Chloride BP ……..50mg

Excipients:

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM:

Syrup

A Clear, green, Coloured liquid with the aroma of Menthol and vanilla.

4. CLINICAL PARTICULARS:

4.1. Therapeutics Indication:

Kofdex® Cough Syrup is indicated for relief of irritating and hacking cough. It is also indicated for symptomatic treatment of cough associated with URTL, bronchitis and pulmonary congestion where retention of tenacious/viscid mucoid secretion is a problem.

4.2. Posology and methods of administration:

Kofdex® Cough Syrup should be taken orally in accordance with dosages stated below:
Dosage:
Adult: 10ml 3-4 times a day
Children (6-12years): 5ml 3-4 times a day
Children (2-6years): 2.5ml 3-4 times a day

Method of administration:
Route of administration: oral
Do not exceed the stated dose. Consult your doctor if symptoms persist after 3days.

4.3. Contraindications:

Dextromethorphan should not be used in patients receiving Monoamine oxidase (MAQ) inhibitors, Bromhexine is contraindicated in the first trimester of pregnancy. Avoid use of Kofdex Syrup in these conditions. The product is contraindicated for use in patients with peptic ulcers.

4.4. Special warning and precautions for use:

Dextromethorphan should be used with caution in sedated, in the debilitated and in patient confined to the supine position. There is no animal or human data concerning the carcinogenic and mutagenic effect or impairment of fertility by this drug.

Pediatric use:
This product should not be used in children under 2years of age because safety for use at that age has not been established. Use with extreme caution in the presence of gastric ulcer

4.5. Interaction with other medicinal products and other forms of interactions:

Kofdex® Cough Syrup 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).
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, diarrhea, and respiratory depression) and development of serotonin syndrome. Potent CYP2D6 enzyme inhibitors include SSRIs such as fluoxetine and 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.

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

Following the administration of bromhexine, the antibiotic concentrations of amoxycillin, erythromycin and oxytetracycline in the sputum and bronchopulmonary secretions are increased. Also, interaction studies with oral anticoagulants or digoxin were not performed. Bromhexine pharmacokinetics are not relevantly affected by co-administration of ampicillin or oxytetracycline. There was also no relevant interaction between bromhexine and erythromycin according to a historical comparison. The lack of any relevant interaction reports during the long-term marketing of the drug suggests no substantial interaction potential with these drugs.

4.6 pregnancy and lactation:

It is not known whether Dextromethorphan is excreted in human milk. Bromhexine is excreted in breast milk. Although unfavorable effects on breastfed infants would not be expected, Caution should be taken when Kofdex® Cough Syrup is administered to nursing woman.

4.7 Effects on ability to drive and use machines:

This medicine can impair cognitive function and can affect a patient's ability to drive safely.

4.8 undesirable effects:

The drug is relatively well tolerated with minor and infrequent side effects. Dextromethorphan occasionally causes slight drowsiness, dizziness and gastrointestinal disturbances. Rarely there may be incidences of nausea and epigastric discomfort. It contraindicated in patients with peptic ulceration.

4.9 Overdose:

Overdose of Dextromethorphan may produce central excitement and mental confusion. Very high doses may produce respiratory depression. Bromhexine dosage above 60mg/day may cause gastric irritation. Treatment of over dosage with the product is essentially symptomatic and supportive. In extreme overdose or individual sensitivity, vital signs including respiration, pulse, blood pressure, temperature and ECG may need to be monitored. Activated charcoal orally or by lavage may be given or sodium/magnesium sulphate orally can be used as cathartic. Attention should be given to the reestablishment of adequate respiratory exchange through provision of patent airway and institution of assisted or control ventilation.
Diazepam may be used to control convulsion, Acidosis and electrolyte losses should be corrected.

5. PHARMACOLOGICAL ACTION:

5.1. Clinical Pharmacology:

Dextromethorphan is a cough suppressant used for the relief on non-productive coughs. It has a central action on cough control centre in medulla and raises the threshold of cough. Dextromethorphan has an antitussive activity equivalent to that of codeine but has no analgesic and non-addictive. In antitussive doses, it shows no effects on respiration, cardiovascular system or the gastrointestinal tract,
Dextromethorphan in therapeutic doses does inhibit ciliary activity and antitussive effect persist for only 5 to 6 hours.
Bromhexine is mucolytic and mucokinetic. It reduces sputum viscosity by breaking down the tenacious network of mucopolysaccharide fibres abundant in mucoid sputum and facilitate ciliary clearance of the sputum. Ammonium chloride produces mild irritation of the mucous lining of the stomach and this gastrovagal reflex increases the respiratory tract fluid, thus relieving dryness and soreness of the respiratory passage. Thus, Bromhexine hydrochloride and Ammonium chloride maintain the integrity of the mucociliary blanket to bring out secretion in normal physiological manner. Menthol acts as a demulcent and soothing agent.

5.2. Pharmacokinetics properties:

Dextromethorphan is rapidly absorbed from the gastrointestinal tract within half an hour following oral administration and exerts its effect for up to 6hours after dosing. Dextromethorphan is metabolized in the liver and excreted in urine both as the unchanged drug and as demethylated metabolites. Bromhexine is bound to plasma proteins. Administration of Bromhexine HCL by mouth to healthy subjects produced peak plasma concentration after about 1 hour and only small amounts were excreted unchanged in the urine with a half-life of about 6.5 hours.

5.3. Metabolism:

Dextromethorphan undergoes rapid and extensive first-pass metabolism in the liver after oral administration. Genetically controlled O-demethylation (CYD2D6) 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. Unmetabolized dextromethorphan, together with the three demethylated morphinan metabolites dextromethorphan (also known as 3-hydroxy-Nmethylmorphinan), 3- hydroxymorphinan and 3-methoxymorphinan have been identified as conjugated products in the urine.

Dextromethorphan, which also has antitussive action, is the main metabolite. In some individual metabolism proceeds more slowly and unchanged dextromethorphan predominates in the blood and urine.
Bromhexine is almost completely metabolized to a variety of hydroxylated metabolites and to dibromanthranilic acid. Ambroxol is a metabolite of bromhexine. There is no pharmacokinetic data available in the elderly or in patients with renal or liver insufficiency. Extensive clinical experience did not give rise to relevant safety concerns in these populations. However, reduced clearance of bromhexine parent substance may be expected in the case of severe liver disease; in the case of severe renal insufficiency, accumulation of metabolites cannot be ruled out.

5.4. Elimination: Dextromethorphan is primarily excreted via the kidney as unchanged parent drug and its active metabolite, dextrorphan. Dextrorphan and 3-hydroxy-morphinan are further metabolized 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 metabolizers is extremely prolonged, in the range of 45 hours.

After administration of radiolabeled bromhexine, about 97.4 ± 1.9% of the dose was recovered in the urine, with less than 1% as the parent compound. Bromhexine plasma concentrations showed a multiexponential decline. After administration of single oral doses between 8 and 32 mg, the terminal half-life of bromhexine ranged between 6.6 and 31.4 hours.

6.0 PHARMACEUTICAL PARTICULARS:

6.1 List of Excipients:

S.NO	Name of the Ingredients	Reference
1.	Menthol	BP
2.	Glycerin	BP
3.	Ethanol 96%	BP
4.	Liquid Sorbitol 70% non-crystallizing	BP
5.	Sodium benzoate	BP
6.	Citric acid Monohydrate	BP
7.	Banana Flavor	IHS
8.	Vanilla Flavor	IHS
9.	Apple green colour	IHS

6.2 Incompatibilities:

Not Applicable.

6.3Shelf life:

36 months

6.4. Special precautions for storage:

Store below 30°C in a dry place. Protect from the light.

6.5. Nature and contents of container:

Kofdex® Cough Syrup container closure system is composed of inner carton containing one piece of 100ml transparent, colorless PET bottle filled with the product and capped with an ROPP cap printed with "unique" logo, with 10ml measuring cup placed on the cap together with pack insert in inner carton.

6.6 Special precautions for disposal and other handling:

After using, dispose of the packaging materials and unused medicines properly. Do not throw wastewater or household waste but dispose properly to protect the environment.

7. APPLICANT/HOLDER OF CERTIFICATE PRODUCT REGISTRATION.

Unique Pharmaceuticals Limited
11, Fatai Atere Way, Matori-Mushin Lagos
Tel: +234 8097421000
Email: mail@uniquepharm.com

8. DRUG PRODUCT MANUFACTURER

Unique Pharmaceuticals Limited
Km 38, Abeokuta Road, Sango-Ota,
Ogun State, Nigeria.
Tel: +234 8097421000
Email: mail@uniquepharm.com

9. NAFDAC REGISTRATION NUMBER(S)

A11-100608

10. DATE OF REVISION OF THE TEXT

20/12/2028