SUMMARY OF PRODUCT CHARACTERISTICS

CORILIEF® DRY Syrup

1. Name of the medicinal product

CORILIEF® DRY Syrup

2. Qualitative and quantitative composition

Each 5 ml contains:
Dextromethorphan hydrobromide 15 mg

Preservatives:
Sodium Benzoate……0.5% m/v

For full list of excipients, see section 6.1

3. Pharmaceutical form

Dark Brown Syrup

4. Clinical particulars

4.1 Therapeutic indications

This product is indicated as an antitussive, for the relief of an unproductive cough.

4.2 Posology and method of administration

Adults and Children aged 12 years and over:
5ml every 4 hours or 10ml every 6 to 8 hours

Children under 12 years:
2.5ml – 5ml every 6 to 8 hours

Children 1 to 6 years
2.5ml every 6 to 8 hours

Method of Administration
For oral use

4.3 Contraindications

This product is contraindicated in individuals with known hypersensitivity to the active substance or to any of the excipients.
This product is contraindicated in individuals who are taking, or have taken, monoamine oxidase inhibitors within the preceding two weeks.

Dextromethorphan, in common with other centrally acting antitussive agents, should not be given to subjects in, or at risk of developing respiratory failure.
This product is contraindicated in patients taking serotonin reuptake inhibitors (SSRIs, see section 4.5).
Not to be used in children under the age of 12 years.

4.4 Special warnings and precautions for use
This product should not be administered to patients with chronic or persistent cough, such as occurs with asthma, or where cough is accompanied by excessive secretions, unless directed by a physician.
There have been no specific studies of this product 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 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.
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.
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.
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
This product contains 6.0 vol % ethanol (alcohol), i.e. up to 240 mg per 5ml equivalent to approximately 6 ml beer, 2.5 ml wine per 5 ml. This can be harmful for those suffering from alcoholism. The ethanol content should be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease or epilepsy.

4.5 Interaction with other medicinal products and other forms of interaction
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 (e.g. hyperpyrexia, hallucinations, gross excitation or coma).

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

4.6 Fertility, pregnancy and lactation
There are no adequate and well-controlled studies in pregnant women. Dextromethorphan should not be used during pregnancy or lactation unless the potential benefit of treatment to the mother outweighs the possible risk to the developing foetus or nursing infant.
It is not known whether dextromethorphan or its metabolites are excreted in breast milk.

4.7 Effects on ability to drive and use machines
Unlikely to produce an effect.
This medicine 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 taking 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:
o The medicine has been taken to treat a medical or dental problem and
o You have taken it according to the information provided with the medicine and
o 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 ≥1/10
Common ≥1/100 and < 1/10
Uncommon ≥1/1,000 and <1/100
Rare ≥1/10,000 and <1/1,000
Very rare <1/10,000, including isolated reports
Not known (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)**
Immune System Disorders	Not known Not known Not known Not known	Angioedema Pruritus Rash Urticaria
Psychiatric Disorders	Not known Not known	Insomnia Confusional state

Nervous System Disorders	Not known Not known Not known Not known	Convulsion Dizziness Psychomotor hyperactivity Somnolence
Respiratory, thoracic and mediastinal Disorders	Not known	Respiratory depression
Gastrointestinal Disorders	Not known Not known Not known Not known Not known	Abdominal pain Diarrhoea Gastrointestinal disturbance Nausea Vomiting

4.9 Overdose

Signs and symptoms

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

Symptoms of overdose may include: mydriasis, nausea and vomiting, CNS depression, excitation, lethargy, nystagmus, psychomotor hyperactivity, serotonin syndrome, somnolence (drowsiness), dizziness, dysarthria (slurred speech), mental confusion, psychotic disorder (psychosis), and respiratory depression.

Management

Treatment should be symptomatic and supportive. Gastric lavage may be of use. Naloxone has been used successfully to reverse central or peripheral opioid effects of dextromethorphan in children (0.01mg/kg body weight).

5. Pharmacological properties

5.1 Pharmacodynamic properties

ATC Code: R05DA09 Pharmacotherapeutic Group: Cough Suppressant, Opium alkaloids and derivatives

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.

5.2 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.

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. 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.

Excretion

Dextromethorphan is primarily excreted via the kidney as unchanged parent drug and its active metabolite, dextrorphan. Dextrorphan and 3-hydroxy-morphinan 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.

5.3 Preclinical safety data

General toxicology

Acute oral toxicity studies conducted with Dextromethorphan report the following LD_{50} values (mg/kg): mouse, 210 and rat, 116. Acute subcutaneous toxicity with Dextromethorphan reports the LD_{50} value (mg/kg): mouse, 112. Acute intravenous toxicity with Dextromethorphan reports the LD_{50} 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.

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

Glycerine
L - Menthol
Povidone K30
Sodium Carboxymethylcellulose
Propylene Glycol
Sodium Citrate
Citric Acid Monohydrate
Sodium Saccharin
Sodium Benzoate
Caramel E150
Liquid Raspberry Flavour R101
Purified Water

6.2 Incompatibilities

None known.

6.3 Shelf life

Two years.

6.4 Special precautions for storage

Do not store above 30 °C.

6.5 Nature and contents of container

100ml in amber glass bottle with polypropylene screw cap
100ml in natural HDPE bottle with LDPE concap

6.6 Special precautions for disposal and other handling

For detailed instructions for use refer to the Patient Information Leaflet in every pack.

7. Applicant

VARICHEM
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8. Principal and Manufacturer

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9. Registration number(s)
TBA

10. Category of Distribution
Pharmacy Only

11. Pharmacological Classification
R05DA09 - Cough Suppressants, Excl. Combinations With Expectorants - Opium alkaloids and derivatives

11.Date of publication
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