SUMMARY OF PRODUCT CHARACTERISTICS.

1. Name of the medicinal product

Dacof Dry Cough Syrup.

2 Qualitative and quantitative composition

Each 5ml contains: Diphenhydramine HCl 12.5mg and Dextromethorphan Hydrobromide 6.5mg

For full list of excipients, see section 6.1.

3.0 Pharmaceutical form: oral syrup for oral administration.

A brown coloured syrup free from visible evidence of contamination.

4.0 Clinical particulars

4.1 Therapeutic indications

This product is indicated as an antitussive, for the night time relief of persistent, dry, irritating cough, and aiding restful sleep.

4.2 Posology and method of administration: For oral administration:

Method of administration

For oral route of administration

Posology:

Adults and children aged 12 years and over:

Patients may start with two 5 ml spoonfuls at bedtime followed by two 5 ml spoonfuls every 6 hours.

Or two 5 ml spoonfuls four times a day.

Do not take more than 4 doses (1 dose = two 5 ml spoonfuls) in 24 hours.

Children under 12 years: This product is contraindicated in children under the age of 12 years

The Elderly:

Normal adult dosage is appropriate

Do not exceed the stated dose.

Keep out of the reach and sight of children.

4.3 Contraindications

This medicine is contraindicated in individuals with known hypersensitivity to the product or any of its components.This medicine is contraindicated in individuals who are taking, or have taken, monoamine oxidase inhibitors within the preceding two weeks. The concomitant use of a dextromethorphan-containing product and monoamine oxidase inhibitors can occasionally result in symptoms such as hyperpyrexia, hallucinations, gross excitation or coma.Dextromethorphan, in common with other centrally acting antitussive agents, should not be given to subjects 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

This product may cause drowsiness; if affected, individuals should not drive or operate machinery.

Diphenhydramine should not be taken by individuals with narrow-angle glaucoma or symptomatic prostatic hypertrophy. Subjects with moderate to severe renal or hepatic dysfunction should exercise caution when using this product (see pharmacokinetics).

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.

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

4.5 Interaction with other medicinal products and other forms of interaction

The concomitant use of a dextromethorphan-containing product and monoamine oxidase inhibitors can occasionally result in symptoms such as hyperpyrexia, hallucinations, gross excitation or coma. 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.This product contains diphenhydramine and therefore may potentiate the effects of alcohol, and other CNS depressants. As diphenhydramine possess some anticholinergic activity, the effects of anticholinergics (e.g. some psychotrophic drugs and atropine) may be potentiated by this product. This may result in tachycardia, mouth dryness, gastrointestinal disturbances (e.g. colic), urinary retention and headache

4.6. Pregnancy and lactation

Both diphenhydramine and dextromethorphan have been in widespread use for many years without apparent ill consequence. However, there is insufficient information on the effects of the administration of dextromethorphan during human pregnancy. In addition, it is not known whether dextromethorphan or its metabolites are excreted in breast milk. Diphenhydramine is known to cross the placenta and has also been detected in breast milk. This medicine 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

This product may cause drowsiness; if affected, individuals should not drive or operate machinery. 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.

4.8 Undesirable effects

Diphenhydramine may cause: drowsiness; dizziness; gastrointestinal disturbance; dry mouth, nose and throat; difficulty in urination or blurred vision.

Dextromethorphan: dizziness, nausea, vomiting, or gastro-intestinal disturbance may occur.

Adverse reactions to menthol at the low concentration present in this medicine are not anticipated.

4.9 Overdose.

Symptoms and signs.

The effects of acute toxicity of this medicine may include drowsiness, hyperpyrexia, anticholinergic effects, lethargy, nystagmus, ataxia, respiratory depression, nausea, vomiting, and hyperactivity. With higher doses, and particularly in children, symptoms of CNS excitation including hallucinations and convulsions may appear; with massive doses, coma or cardiovascular collapse may follow.

Treatment

Treatment of overdose should be symptomatic and supportive. Measures to promote rapid gastric emptying (with syrup of ipecac-induced emesis or gastric lavage) and, in cases of acute poisoning, the use of activated charcoal, may be useful. The intravenous use of physostigmine may be efficacious in antagonizing severe anticholinergic symptoms. Naloxone has been used successfully as a specific antagonist to dextromethorphan toxicity in children. Convulsions may be controlled with diazepam and thiopental sodium.

5. 0 Pharmacological properties

5.1 Pharmacodynamic properties.

Pharmacotherapeutic group:

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. A single oral dose of 10-20mg dextromethorphan produces its antitussive action within 1 hour and lasts for at least 4 hours. Diphenhydramine possesses antitussive, antihistaminic, and anticholinergic properties. Experiments have shown that the antitussive effect (resulting from an action on the brainstem) is discrete from its antihistaminic effect. The duration of activity of diphenhydramine is between 4 and 8 hours.

5.2 Pharmacokinetic properties

Diphenhydramine, dextromethorphan and menthol are well absorbed from the gut following oral administration. Peak serum levels of diphenhydramine following a 50 mg oral dose are reached at between 2 and 2.5 hrs after an oral dose. Due to individual differences in the metabolism of dextromethorphan. After the administration of a 20 mg dose of dextromethorphan to healthy volunteers, the Cmax varied from < 1 µg/l to 8 µg/l, occurring within 2.5 hrs of administration.

Distribution

Diphenhydramine is widely distributed throughout the body, including the CNS. Following a 50 mg oral dose of diphenhydramine, the volume of distribution is in the range 3.3 - 6.8 L/kg and it is some 78% bound to plasma proteins.

Dextromethorphan

Due to extensive pre-systemic metabolism by the liver, detailed analysis of the distribution of orally administered dextromethorphan is not possible.

Metabolism and elimination

Diphenhydramine undergoes extensive first pass metabolism. Two successive N-demethylations occur, with the resultant amine being oxidized to a carboxylic acid. Values for plasma clearance of a 50 mg oral dose of diphenhydramine lie in the range 600 - 1300 ml/min, and the terminal elimination half-life lies in the range 3.4 - 9.3 hours. Little unchanged drug is excreted in the urine. Dextromethorphan undergoes rapid and extensive first-pass metabolism in the liver after oral administration. Genetically controlled O-demethylations (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.

5.3 Preclinical safety data

The active ingredients of this medicine are well-known constituents of medical products and their safety profiles are well documented.

6.0**Pharmaceutical particulars**

6.1 List of excipients

Menthol crystals,
Sodium Methyl Paraben,
Sodium Propyl Paraben,
Sodium Saccharin,
White refined Sugar,
Glycerin,
Neutral spirit,
Bronopol,
Citric Acid,
Natrosol HHR 250,

Sunset yellow colour,
Vanilla flavour liquid,
Lake indigo carmine colour,
Monopropylene Glycol
Purified Water.

6.2 Incompatibilities

None known

6.3 Shelf life

36 months from the date of manufacture. (3 years)

6.4 Special precautions for storage

Store in a dry place, below 30°C. Protected from light

Keep all medicines out of reach of children.

6.5 Nature **and contents of container**

100ml amber coloured PET bottles in a unit box, along with a literature insert.

6.6 Special precautions for disposal and other handling

No special requirements.

7.0 **Marketing authorization holder/Registrant**.

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9.0 **Date of revision of the text:**

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