SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Medorphan 1.5 mg/ml syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 1.5 mg dextromethorphan hydrobromide.
Excipients with known effect: Each ml contains sucrose 325 mg, sorbitol liquid 65 mg, liquid glucose 395 mg, ethanol 50.28 mg, sodium benzoate 0.6 mg, propylene glycol 2.652 mg and benzyl alcohol as part of the flavouring agent.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Syrup.
The solution is a slightly yellowish, clear, peach flavored syrup.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Medorphan is indicated in adults and children 12 years and older, for the relief of an unproductive cough.

4.2 Posology and method of administration

Posology
Adults
10 ml syrup (15 mg dextromethorphan) 3-4 times a day.
Maximum daily dose: 40 ml syrup (60 mg dextromethorphan)

Paediatric population
Children aged 12 years and over: As for adults above.
Children under 12 years: Medorphan is not intended in children under the age of 12 years.

Elderly (over 65 years)
As for adults above.

Hepatic/renal dysfunction
Due to the extensive hepatic metabolism of dextromethorphan, caution should be exercised in the presence of hepatic impairment (see sections 4.4 and 5.2).

Do not exceed the stated dose.

Method of administration
Oral.
Treatment should not exceed a period longer than 2-3 weeks.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Dextromethorphan should not be used in 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 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).
Patients with respiratory insufficiency, or at risk of developing respiratory failure (see section 4.4).
In patients taking serotonin reuptake inhibitors (SSRIs, see section 4.5).
Medorphan is contraindicated for use in children under 12 years of age.

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.

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.

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

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.

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

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).

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 Medorphan should be discontinued.

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

Warnings related to the excipients

Medorphan also contains sucrose, sorbitol liquid (E420), liquid glucose, ethanol, sodium, sodium benzoate (E211), propylene glycol (E1520) and benzyl alcohol:
This medicine contains 3.25 g of sucrose per dose (10 ml). Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. This should be taken into account in patients with diabetes mellitus.
This medicine contains 0.65 g of sorbitol per dose (10 ml). Patients with hereditary fructose intolerance (HFI) should not take this medicinal product.
This medicine contains 3.95 g of glucose per dose 10 ml. Patients with rare hereditary problems of problems of galactose intolerance e.g. galactosaemia or glucose galactose malabsorption should not take this medicine. This should be taken into account in patients with diabetes mellitus.

This medicine contains 503 mg of alcohol (ethanol) in each 10 ml, which is equivalent to 5.03vol%. The amount in 10 ml of this medicine is equivalent to less than 10 ml beer or 4.5 ml wine. The small amount of alcohol in this medicine will not have any noticeable effects.
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'.
This medicine contains 6 mg sodium benzoate in each 10 ml.
This medicine contains 26.52 mg propylene glycol (E1520) in each 10 ml.
This medicine contains negligible amount of benzyl alcohol as part of the flavouring agents in each 10 ml. Benzyl alcohol may cause allergic reactions.

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 (e.g. hyperpyrexia, hypertension, arrhythmias, 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.

Metoprolol
Metoprolol is a CYP2D6 substrate and metabolism of dextromethorphan has been shown to be prolonged when the two drugs are administered concomitantly.

Isavuconazole

Isavuconazole is a moderate inhibitor of CYP3A4 and a mild inducer of CYP2B6. When administered concomitantly with dextromethorphan, the AUC and Cmax of dextromethorphan has been observed to increase by 18% and 17%, respectively.

CNS depressants

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

Pregnancy

There are no adequate and well-controlled studies in pregnant women.

Dextromethorphan should not be used during pregnancy unless the potential benefit of treatment to the mother outweighs the possible risk to the developing foetus.

Breast-feeding

It is not known whether dextromethorphan or its metabolites are excreted in breast milk.

Dextromethorphan should not be used during lactation unless the potential benefit of treatment to the mother outweighs the possible risk to the developing nursing infant.

Fertility

There are no reported effects of the use of dextromethorphan on fertility. Pre-clinical experience is limited (see section 5.3).

4.7 Effects on ability to drive and use machines

Although the overall data do not support that dextromethorphan impacts driving, due to its potential for somnolence and dizziness, caution should be used when driving a motor vehicle or operating machinery.

4.8 Undesirable effects

Adverse drug reactions (ADRs) identified during clinical trials and postmarketing 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, <1/10); uncommon (≥1/1,000, < 1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000); 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'.

System Organ Class	Frequency	Adverse Drug Reaction
Immune system disorder	Not Known	Angioedema
Skin and subcutaneous tissue disorders	Not Known	Pruritus
	Not Known	Rash
	Not Known	Urticaria
Psychiatric disorders	Rare	Confusional state
	Not known	Insomnia
	Not known	Agitation
Nervous system disorders	Not known	Convulsion
	Not known	Dizziness
	Not known	Psychomotor hyperactivity
	Not known	Somnolence
Respiratory, thoracic and mediastinal disorders	Rare	Bronchoconstriction
	Rare	Dyspnoea
	Not known	Respiratory depression
Gastrointestinal disorders	Not known	Abdominal pain
	Not known	Diarrhoea
	Not known	Gastrointestinal disturbance
	Not known	Nausea
	Not known	Vomiting

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 national reporting system.

4.9 Overdose

Signs and symptoms

Dextromethorphan overdose may be associated with nausea, vomiting, dystonia, agitation, confusion, somnolence, stupor, nystagmus, cardiotoxicity (tachycardia, abnormal ECG including QTc prolongation), ataxia, toxic psychosis with visual hallucinations, hyperexcitability.
In the event of massive overdose the following symptoms may be observed: coma, respiratory depression, convulsions.
Dextromethorphan overdose is also associated with conversion disorder; hallucinations, mixed; clumsiness; depressed level of consciousness; dizziness; dysarthria; lethargy; hypertension; serotonin syndrome; tremor; miosis; mydriasis; urinary retention and ischaemic colitis.
Bromide intoxication has been observed during concomitant use with bromide-containing over-the-counter drugs or with overdose of dextromethorphan hydrobromide.

Management
Treatment of overdose 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 (0.01 mg/kg body weight).
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.
Benzodiazepines for seizures and benzodiazepines and external cooling measures for hyperthermia from serotonin syndrome can be used.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cough and cold preparations, Cough suppressants, excl. combinations with expectorants, Opium alkaloids and derivatives, ATC code: R05DA09.

Dextromethorphan is the dextrorotatory isomer of 3-methoxy-N-methylmorphinan. 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.

Biotransformation

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.

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.

5.3 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.

Carcinogenicity
There are no known reports of animal carcinogenicity studies for Dextromethorphan. There is no evidence of a carcinogenic risk to humans. The overall weight of evidence for Dextromethorphan and its structural analogues, support the conclusion that this class of phenanthrenebased chemicals, and Dextromethorphan, in particular, are not genotoxic *in vitro* or *in vivo*, and do not represent a carcinogenic risk to patients.

Teratogenicity
There was no association between dextromethorphan and malformations, dextromethorphan is generally considered safe to use during pregnancy.

Fertility

Mating, gestation, fertility, littering and lactation were studied in rats at doses up to 50 mg/kg and no adverse effects were found. There is no evidence of a fertility impairment risk to humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Saccharin Sodium
- Sodium Benzoate (E211)
- Sucrose
- Glucose liquid spray dried
- Sorbitol liquid (E420) (non-crystallising)
- Glycerol (E422)
- Ethanol anhydrous
- Levomenthol
- Citric acid
- Caramel flavour (contains propylene glycol (E1520), benzyl alcohol)
- Peach flavour (contains propylene glycol (E1520), sodium citrate, benzyl alcohol, limonene)
- Purified Water

6.2 Incompatibilities

None known.

6.3 Shelf life

3 years

After first opening: Until the expiry date stated on the label

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

150 ml or 200 ml Type III (Ph.Eur) brown glass bottles closed with one of the following caps:

- Aluminium cap. A plastic measuring spoon with graduations of 2.5ml and 5ml is provided as part of the pack.
- Plastic tamper evident cap. A plastic measuring cup with graduation of 5ml, 10ml, 15ml and 20ml is provided as part of the pack.
- Plastic child proof cap. A plastic measuring cup with graduation of 2ml, 2.5ml, 3ml, 4ml, 5ml, 6ml, 7ml, 7.5ml, 8ml, 9ml, 10ml, 11ml, 12ml, 12.5ml and 15ml is provided as part of the pack.

6.6 Special precautions for disposal and other handling

No special requirements
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER

07355/08864/NMR/2021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04/05/2022
Date of latest renewal: N/A

10. DATE OF REVISION OF THE TEXT

11/2022