SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Medofed Compound Oral Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of Medofed Compound oral solution contains 100 mg Guaifenesin, 15 mg Dextromethorphan hydrobromide, 20 mg Pseudoephedrine hydrochloride and 1.25 mg Triprolidine hydrochloride.

Excipients with known effect: propylene glycol, sucrose, sorbitol.
Each 5 ml of Medofed Compound contain 250 mg propylene glycol, 1150 mg sucrose and 2960 mg sorbitol 70%.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral Solution.
Red, clear, flavored solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Medofed Compound is indicated for the symptomatic relief of upper respiratory tract disorders accompanied by productive or dry cough, which benefit from the administration of a nasal decongestant, a histamine H_1 receptor antagonist, an antitussive and an expectorant combination.

4.2 Posology and method of administration

Posology
Adults: 10 ml every 4 - 6 hours up to 4 times a day.

Paediatric population

- Children over 12 years: as for adults.
- Children 6 - 12 years: 5 ml every 4 - 6 hours up to 4 times a day.
- Children 2 - 5 years: 2.5 ml every 4 - 6 hours up to 4 times a day.

- Children under 2 years old: Not recommended.

Use in the elderly

No specific studies have been carried out in the elderly, but triprolidine and pseudoephedrine have been widely used in older people.

Hepatic impairment

Caution should be exercised when administering Medofed Compound to patients with severe hepatic impairment.

Renal impairment

Caution should be exercised when administering Medofed Compound to patients with moderate to severe renal impairment.

Method of administration

Oral administration. Measuring spoon is provided inside the carton box.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Individuals who are taking or have taken monoamine oxidase inhibitors within the preceding two weeks. The concomitant use of pseudoephedrine and this type of product may occasionally cause a rise in blood pressure (see section 4.5).

Patients with severe hypertension or severe coronary artery disease.

Concurrent administration of Medofed Compound and furazolidone (see section 4.5).

Medofed Compound should not be administered to patients where cough is associated with asthma or where cough is accompanied by excessive secretions.

Dextromethorphan, in common with other centrally acting antitussive agents, should not be given to patients in, or at risk of developing respiratory failure.

4.4 Special warnings and precautions for use

Ischaemic colitis

Some cases of ischaemic colitis have been reported with pseudoephedrine. Pseudoephedrine should be discontinued and medical advice sought if sudden abdominal pain, rectal bleeding or other symptoms of ischaemic colitis develop.

Ischaemic optic neuropathy

Cases of ischaemic optic neuropathy have been reported with pseudoephedrine.
Pseudoephedrine should be discontinued if sudden loss of vision or decreased visual acuity such as scotoma occurs.

Severe Skin reactions

Severe skin reactions such as acute generalized exanthematous pustulosis (AGEP) may occur with pseudoephedrine-containing products. This acute pustular eruption may occur within the first 2 days of treatment, with fever, and numerous, small, mostly non-follicular pustules arising on a widespread oedematous erythema and mainly localized on the skin folds, trunk, and upper extremities. Patients should be carefully monitored. If signs and symptoms such as pyrexia, erythema, or many small pustules are observed, administration of Medofed Compound should be discontinued and appropriate measures taken if needed.

Medofed Compound may cause drowsiness and impair performance in tests of auditory vigilance (see section 4.7).

Although there are no objective data, users of Medofed Compound should avoid the concomitant use of alcohol or other centrally acting sedatives (see section 4.5).

Although pseudoephedrine has virtually no pressor effects in patients with normal blood pressure, Medofed Compound should be used with caution in patients taking antihypertensive agents, tricyclic antidepressants, other sympathomimetic agents, such as decongestants, appetite suppressants and amphetamine-like psychostimulants. The effects of a single dose on the blood pressure of these patients should be observed before recommending repeated or unsupervised treatment (see section 4.5).

As with other sympathomimetic agents, caution should be exercised in patients with uncontrolled diabetes, hyperthyroidism, elevated intraocular pressure, hypertension, heart disease and prostatic enlargement.

There have been no specific studies of Medofed Compound in patients with hepatic and/or renal dysfunction. Caution should be exercised in the presence of severe renal or 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.

Medofed Compound should not be used for persistent or chronic cough, such as occurs with asthma, or where cough is accompanied by excessive secretions, unless directed by a physician.

If urine is collected within 24 hours of a dose of Medofed Compound, a metabolite of guaiphenesin may cause a colour interference with laboratory determinations of urinary 5-hydroxyindoleacetic acid (5-HIAA) and vanillylmandelic acid (VMA).

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 medicine contains 250 mg propylene glycol in each 5 ml oral solution.
This medicine contains 2960 mg sorbitol 70% in each 5 ml oral solution. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account. The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product. Sorbitol may cause gastrointestinal discomfort and mild laxative effect.
This medicine contains 1150 mg sucrose in each 5 ml oral solution. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of Medofed Compound with sympathomimetic agents (such as decongestants, appetite suppressants and amphetamine-like psychostimulants) or with monoamine oxidase inhibitors, which interfere with the catabolism of sympathomimetic amines, may occasionally cause a rise in blood pressure (See section 4.3 and 4.4).

The antibacterial agent furazolidone is known to cause a dose-related inhibition of monoamine oxidase. Although there are no reports of hypertensive crises caused by the concurrent administration of Medofed Compound and furazolidone, they should not be taken together.

Because of its pseudoephedrine content, Medofed Compound may partially reverse the hypotensive action of drugs which interfere with sympathetic activity including bretylium bethanidine, guanethidine, debrisoquine, methyldopa, alpha and beta-adrenergic blocking agents. (See section 4.4).

Although there are no objective data, users of Medofed Compound should avoid concomitant use of alcohol or other centrally acting sedatives (see section 4.4).

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

Pregnancy

Although pseudoephedrine and triprolidine have been in widespread use for many years without apparent ill consequence, there are no specific data on their use during pregnancy. Caution should therefore be exercised by balancing the potential benefit of treatment to the mother against any possible hazards to the developing foetus.

In rats and rabbits systemic administration of triprolidine up to 75 times the human dose did not produce teratogenic effects. Systemic administration of pseudoephedrine, up to 50 times the human dose in rats and up to 35 times the human dose in rabbits, did not produce teratogenic effects.
Insufficient information is available on the effects of administration of Medofed Compound during human pregnancy. Like most medicines, it should not be used during pregnancy unless the potential benefit of treatment to the mother outweighs any possible risk to the developing foetus.

Breast-feeding

Pseudoephedrine and triprolidine are excreted in breast milk in small amounts but the effect of this on breast fed infants is not known. It has been estimated that 0.5 - 0.7% of a single dose of pseudoephedrine ingested by a mother will be excreted in the breast milk over 24 hours.
It is not known whether dextromethorphan or its metabolites are excreted in breast milk.
Guaiphenesin is excreted in breast milk in small amounts with no effect expected on the infant.

Fertility
No studies have been conducted in animals to determine whether triprolidine or pseudoephedrine have potential to impair fertility. There is no information on the effect of Medofed Compound on human fertility.

4.7 Effects on ability to drive and use machines

Medofed Compound may cause drowsiness and impair performance in tests of auditory vigilance. Patients should not drive a vehicle or operate machinery until they have determined their own response.

4.8 Undesirable effects

Adverse reactions are listed below, by system organ class and by frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from available data).

Psychiatric disorders
Rare: hallucinations.
Not known: Central nervous system (CNS) depression or excitation, sleep disturbance

Nervous system disorders
Very common: drowsiness (reported most frequently).

Eye disorders
Not known: Ischaemic optic neuropathy.

Gastrointestinal disorders
Uncommon: Side effects attributed to dextromethorphan are uncommon; occasionally nausea, vomiting or gastro-intestinal disturbance may occur.

Not known: Ischaemic colitis.

Skin and subcutaneous tissue disorders
Uncommon: Skin rashes with or without irritation.
Not known: Severe skin reactions, including acute generalized exanthematous pustulosis (AGEP).

Respiratory, thoracic and mediastinal disorders
Uncommon: dryness of mouth, nose and throat.

Cardiac disorders
Uncommon: tachycardia.

Renal and urinary disorders
Uncommon: Urinary retention has been reported occasionally in men receiving pseudoephedrine, prostatic enlargement could have been an important predisposing factor.

Side effects resulting from guaiphenesin administration are very rare.

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

Symptoms
The effects of acute toxicity from Medofed Compound may include drowsiness, lethargy, dizziness, ataxia, weakness, hypotonicity, respiratory depression, dryness of the skin and mucous membranes, tachycardia, hypertension, palpitations hyperpyrexia, hyperactivity, irritability, convulsions, tremor and difficulty with micturition, nausea and vomiting.

Management
Necessary measures should be taken to maintain and support respiration and control convulsions. Gastric lavage should be performed up to 3 hours after ingestion if indicated. Catheterisation of the bladder may be necessary. If desired, the elimination of pseudoephedrine can be accelerated by acid diuresis or by dialysis.

Naloxone has been used successfully as a specific antagonist to dextromethorphan toxicity in children.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opium derivatives and expectorants, ATC code: R05FA02

Pseudoephedrine

Pseudoephedrine has a direct and indirect sympathomimetic activity and is an orally effective upper respiratory tract decongestant. Pseudoephedrine is substantially less potent than ephedrine in producing both tachycardia and elevation in systolic blood pressure and considerably less potent in causing stimulation of the central nervous system. Pseudoephedrine produces its decongestant effect within 30 minutes, persisting for at least 4 hours.

Triprolidine

Triprolidine provides antihistamine activity by antagonising H1 receptors. Triprolidine provides symptomatic relief in conditions believed to depend wholly or partially upon the triggered release of histamine. It is a potent competitive histamine H_1-receptor antagonist of the pyrrolidine class with mild central nervous system depressant properties which may cause drowsiness. After oral administration of a single dose of 2.5 mg triprolidine to adults, the onset of action as determined by the ability to antagonise histamine-induced weals and flares in the skin is within 1 to 2 hours. Peak effects occur at about 3 hours and, although activity declines thereafter, significant inhibition of histamine-induced weals and flares still occur 8 hours after the dose.

Dextromethorphan

Dextromethorphan has an antitussive action. It controls coughs by spasms by depressing the medullary cough centre.

Guaiphenesin

Guaiphenesin is thought to exert its pharmacological action by stimulating receptors in the gastric mucosa. This increases the output from secretory glands of the gastrointestinal system and reflexly increases the flow of fluids from glands lining the respiratory tract. The result is an increase in volume and decrease in viscosity of bronchial secretions. Other actions may include stimulating vagal nerve endings in bronchial secretory glands and stimulating certain centres in the brain which in turn enhance respiratory fluid flow. Guaiphenesin produces its expectorant action within 24 hours.

5.2 Pharmacokinetic properties

Pseudoephedrine

Pseudoephedrine is rapidly and completely absorbed after oral administration. After an oral dose of 180 mg to man, peak plasma concentrations of 500-900 ng/ml were obtained about 2 hours post dose. The plasma half life was approximately 5.5 hours and was increased in subjects with alkaline urine and decreased in subjects with acid urine. The apparent volume of distribution of pseudoephedrine (vd/f) was approximately 2.8 l/kg.

Pseudoephedrine is partly metabolised in the liver by n-demethylation to norpseudoephedrine, an active metabolite. Pseudoephedrine and its metabolite are excreted in the urine; 55% to 90% of a dose is excreted and unchanged. The apparent total body clearance of pseudoephedrine (c1/f) was approximately 7.5 ml/nim/kg. The elimination rate constant (k_{el}) was approximately 0.13 hr^{-1}. The rate of urinary elimination is accelerated when the urine is acidified. Conversely, as the urine pH increases, the rate of urinary elimination is slowed. Excretion was mainly via the urine.

Triprolidine

In common with other antihistamines, triprolidine hydrochloride is rapidly absorbed, peak plasma levels being observed 2 hours after an oral dose, metabolised in the liver and excreted, mainly as metabolites in the urine. The plasma half life is approximately 3.2 hours. In pharmacokinetic studies, the apparent volume of distribution of triprolidine was approximately 6.5 l/kg for the tablet formulation and 7.5 l/kg for the syrup. Animal hepatic microsomal enzyme studies have revealed the presence of several triprolidine metabolites with an oxidised product of the toluene methyl group predominating. In man, it has been reported that only about 1% of an administered dose is eliminated as unchanged triprolidine over a 24-hour period. The apparent total body clearance of triprolidine (cl/f) was approximately 30-37 ml/min/kg. The elimination rate constant (k_{el}) was approximately 0.26 hr^{-1}

Dextromethorphan

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.

Guaiphenesin

Guaiphenesin is well absorbed from the gastro-intestinal tract following oral administration, although limited information is available on its pharmacokinetics. No information is available on the distribution of guaiphenesin in humans. Guaiphenesin appears to undergo both oxidation and demethylation. Following an oral dose of 600 mg guaiphenesin to 3 healthy male volunteers, the T½ was approximately 1 hour and the drug was not detectable in the blood after approximately 8 hours.

5.3 Preclinical safety data

The active ingredients are well-known constituents of medicinal products and their safety profiles are well documented. The results of pre-clinical studies do not add anything of relevance for therapeutic purposes.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Propylene glycol,
- glycerol,
- sorbitol 70%,
- sodium benzoate,
- sucrose,
- sodium saccharin,
- citric acid,
- ponceau red E124,
- acacia gum,
- ethanol absolute,
- peppermint oil,
- cherry Morella
- purified water.

6.2 Incompatibilities

None known.

6.3 Shelf-life

60 months.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Amber glass bottles having metal roll-on closures or plastic screw caps. Each cap type is pilfar proof lined with atoxic polyvinyl chloride liner. Bottles containing either 100 ml, 150 ml or 200 ml of Medofed Compound are available. Measuring spoon is provided inside the carton box.
Not all pack sizes may be available.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

MEDOCHEMIE LTD, 1-10 Constantinoupoleos street, 3011 Limassol, Cyprus

8. MARKETING AUTHORISATION NUMBER

04354/06955/REN/2019

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02/06/2015
Date of latest renewal: 16/07/2020

10. DATE OF REVISION OF THE TEXT

05/2020