SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Covonia Night Time Formula

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Dextromethorphan Hydrobromide Ph.Eur. 6.65mg/5ml (Recommended dose is 15ml)

Diphenhydramine Hydrochloride Ph.Eur. 10.0mg/5ml (Recommended dose is 15ml)

Excipients with known effect

This medicine contains, per 15ml dose: 2.7g Maltitol, 3.675g Sorbitol, 880mg Ethanol, 18mg Sodium benzoate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral Solution

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the night time symptomatic relief of unproductive cough and congestive symptoms associated with colds.

4.2 Posology and method of administration

Posology
Adults, the Elderly and Children over 12 years
3 x 5ml spoonfuls at bedtime. Repeat after 6 hours if required.

Children under 12 years
Do not give to children under 12 years old.

4.3 Contraindications

Contraindicated in known hypersensitivity to any of the ingredients. Contraindicated in persons under treatment with monoamine oxidase inhibitors or within 2 weeks of discontinuation of MAOI use.

Contraindicated in persons under treatment with selective serotonin reuptake inhibitors (SSRIs)

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

Covonia Night Time Formula should not be used in liver dysfunction. It should not be administered to patients where cough is associated with asthma, or patients with productive cough.

Diphenhydramine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Do not give to children under 12 years old.

4.4 Special warnings and precautions for use

Because of their antimuscarinic properties antihistamines should be used with care in conditions such as closed angle glaucoma, urinary retention, prostatic hyperplasia or pyeloduodenal obstruction. Caution should also be exercised in patients with epilepsy or severe cardiovascular disorders. Caution is needed for the use of dextromethorphan in patients with a history of asthma, or with chronic or persistent cough. This medicine should be used with caution in atopic children due to histamine release.
Use of dextromethorphan with alcohol or other CNS depressants may increase the effects on the CNS and cause toxicity in relatively small doses (see section 4.5).

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).
<u>Labels will state:</u>
If symptoms persist consult your doctor.
Keep out of the sight and reach of children.
Do not take more medicine than the label tells you to.
Do not take with any other cough and cold medicine
Warning: This medicine may make you feel sleepy. If this happens do not drive or use tools or machines. Do not drink alcohol.
Can cause addiction.
This medicine may cause opioid-like effects when used at high doses.

<u>Drug dependence, tolerance and potential for abuse</u>

For all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals

with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).

Drug withdrawal syndrome

The drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

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 Covonia Night Time Formula should be discontinued.

Ingredients with specified warnings

This medicine contains less than 1mmol sodium (23mg) per 15ml dose, that is to say essentially ‘sodium-free’.

This medicine contains 18mg Sodium benzoate in each 15ml dose.

This medicine contains maltitol and 3.675g Sorbitol in each 15ml dose. Patients with rare hereditary fructose intolerance (HFI) should not take/be given this medicinal product.
This medicine contains 880mg of alcohol (ethanol) in each 15ml dose. The amount in 15ml of this medicine is equivalent to less than 22ml of beer or 9ml of wine. The small amount of alcohol in this medicine is unlikely to have any noticeable effects.

4.5 Interaction with other medicinal products and other forms of interaction

Dextromethorphan and diphenhydramine should not be used in persons under treatment with monoamine oxidase inhibitors or within 2 weeks of discontinuation of MAOI use in view of the potential risk of serotonin syndrome and a severe or fatal interaction (see section 4.3).
Dextromethorphan-specific interactions
Avoid use of dextromethorphan with moclobemide or other reversible MAO-A inhibitors; rasagiline or other MAO-B inhibitors.

Manufacturer of memantine advises avoid concomitant use with dextromethorphan.
Dextromethorphan might exhibit additive CNS depressant effects when co-administered with alcohol, antihistamines, psychotropics, and other CNS depressant drugs.
Cimetidine inhibits the metabolism of opioid analgesics.
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 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, SSRIs (including sertraline, see section 4.3), 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.

Diphenhydramine-specific interactions
Diphenhydramine as an antihistamine has additive sedative effects with alcohol and other CNS depressants including barbiturates, hypnotics, opioid analgesics, anxiolytic sedatives and antipsychotics. It may also have additive antimuscarinic effects with antimuscarinic drugs such as atropine and some antidepressants.
Diphenhydramine as an antihistamine may theoretically antagonise the effect of histamine and betahistine.
Diphenhydramine inhibits the cytochrome P450 isoenzyme CYP2D6 and may affect the metabolism of some beta blockers and the anti depressant venlafaxine.

4.6 Pregnancy and Lactation

Although dextromethorphan and diphenhydramine have been in widespread use for many years, insufficient data are available on their use during pregnancy. Use during pregnancy is inadvisable unless there is a clear need. Caution should, therefore, be exercised by balancing the potential benefits of treatment against any possible hazards.

It is not known if dextromethorphan or its metabolites are excreted in human breast milk. Diphenhydramine is excreted in breast milk but the amount has not been quantified. Covonia Night Time Formula is, therefore, best avoided during breast feeding.

4.7. Effects on ability to drive and use machines

Diphenhydramine may cause drowsiness, persons so affected should be advised not to drive or to 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 prescribing 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:
  - The medicine has been prescribed to treat a medical or dental problem and
  - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
  - It was not affecting your ability to drive safely

4.8 Undesirable effects

The following undesirable effects have been reported for use of dextromethorphan or sedating antihistamines including diphenhydramine, and may arise from use of Covonia Night Time Formula. The frequency of adverse effects cannot be estimated from available data.

Undesirable effects may be attributable to both dextromethorphan and sedating antihistamines unless otherwise stated.

Blood and the lymphatic system disorders:	Blood disorders including agranulocytosis, leucopenia, haemolytic anaemia, and thrombocytopenia (attributable to sedating antihistamines)
Psychiatric disorders:	Confusion
	Excitation (attributable to dextromethorphan)
	depression (attributable to sedating antihistamines)
	Drug dependence (see section 4.4)
Nervous system disorders:	Drowsiness and lowered ability to concentrate, dizziness, convulsions
	Extrapyramidal effects, paradoxical stimulation,

	headache, psychomotor impairment, tremor, paraesthesias, sleep disturbances (attributable to sedating antihistamines)
Eye disorders:	Blurred vision, angle-closure glaucoma (attributable to sedating antihistamines)
Ear and labyrinth disorders:	Tinnitus (attributable to sedating antihistamines)
Cardiac disorders:	Palpitations, arrhythmias (attributable to sedating antihistamines)
Vascular disorders:	Hypotension (attributable to sedating antihistamines)
Respiratory, thoracic and mediastinal disorders:	Respiratory depression (attributable to dextromethorphan)
	Thickened respiratory tract secretions, Bronchospasm (attributable to sedating antihistamines)
Gastrointestinal disorders:	Gastrointestinal disturbances (including nausea, vomiting, diarrhoea)
	Dry mouth (attributable to sedating antihistamines)
Hepatobiliary disorders:	Liver dysfunction (attributable to sedating antihistamines)
Skin and subcutaneous tissue disorders:	Hypersensitivity reactions including skin rash
	Angioedema, sweating, hair loss (attributable to sedating antihistamines)
Musculoskeletal, connective tissue and bone disorders:	Myalgia (attributable to sedating antihistamines)
Renal and urinary disorders:	Urinary retention (attributable to sedating antihistamines)

General disorders and administration site conditions:	Anaphylaxis (attributable to sedating antihistamines) Drug withdrawal syndrome

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 Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' in the Google Play or Apple App Store.

4.9 Overdose

Acute overdose of dextromethorphan does not usually result in serious signs and symptoms unless very large amounts have been ingested. It is thought to be of low toxicity, but the effects in overdosage will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs. Signs and symptoms of substantial overdose may include nausea and vomiting, CNS disturbances (hyperexcitability, irritability, mental confusion, lethargy, somnolence, ataxia, auditory and visual hallucinations, psychotic disorder), dizziness, slurred speech, nystagmus and respiratory depression.

Symptoms and signs:

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.

Management:

-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.

Mild cases of diphenhydramine overdose are mainly characterised by prominent antimuscarinic effects including dry mouth, headache, nausea, tachycardia and urinary retention. Larger doses produce depression or stimulation of the CNS. In small children, the stimulatory effects predominate and clinical features include hallucinations and convulsions. Adults usually develop drowsiness first, then convulse and lapse into coma at later stage. Fever and flushing is seen in children but is uncommon in adults.

Gastric lavage should be used if indicated. Naloxone has been used successfully as a specific antagonist to dextromethorphan toxicity in children (0.01mg/kg body weight). Convulsions can be controlled with diazepam. Other treatment is supportive and symptomatic and may include artificial respiration, external cooling for hyperpyrexia and intravenous fluids.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: RO5 DA – Opium Alkaloids and Derivatives

Dextromethorphan
Dextromethorphan is a non-opioid, centrally acting cough suppressant. It raises the threshold for the cough reflex in the medulla oblongata. In therapeutic doses, it has no significant analgesic, respiratory depressant, euphoriant or dependence-producing properties. It does not inhibit ciliary function.

Diphenhydramine
Diphenhydramine is an ethanolamine H_1 histamine receptor antagonist. It possesses antitussive, sedative, antimuscarinic and antiemetic properties. Antihistamines, like diphenhydramine, are useful for controlling nasal itching, sneezing and rhinorrhoea but are less effective for the relief of nasal congestion.

5.2 Pharmacokinetic properties

Dextromethorphan
Dextromethorphan is rapidly absorbed from the gastrointestinal tract following oral administration. It is subject to extensive presystematic metabolism resulting in very low peak plasma concentrations of 1.8ng/ml within 2.5 hours of an oral dose. Peak concentrations of the main metabolite, dextrophan occur 1-2 hours after ingestion. The terminal plasma elimination half-life of dextrophan is about three hours.
It is not known if dextromethorphan or dextrophan is excreted into breast milk or crosses the placenta.
Dextromethorphan undergoes rapid and extensive first-pass metabolism in the liver after oral administration. Genetically controlled O-demethylation (including the cytochrome P450 2D6 isozyme (CYP2D6), which is then conjugated by UDP-glucuronosyl transferases) 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-Nmethylmorphinan), 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.
Less than 1% of the dose of dextromethorphan is excreted in the faeces. Urinary excretion of parent drug and metabolites accounts for up to 50% of the ingested dose over 24 hours.
Diphenhydramine
Diphenhydramine is well absorbed from the gastrointestinal tract but its availability varies between 26 and 60% due to first pass metabolism. Peak plasma concentrations are achieved about 1 to 4 hours after oral administration. The plasma elimination half-life is 3.3 hours.
Diphenhydramine is widely distributed throughout the body including the CNS. It crosses the placenta and has been detected in breast milk. It is highly (85-98%) bound to plasma proteins.

Orientals have lower plasma levels, lower protein binding and a higher volume of distribution and higher plasma clearance, but not half-life, than Caucasians.
Diphenhydramine is extensively metabolised mainly in the liver. It is N-demethylated to monodesmethyldiphenhydramine and didesmethyl-diphenhydramine. The resultant primary amine is oxidatively deaminated to yield the carboxylic acid, diphenylmethoxy acetic acid which may be conjugated with glutamine or glycine.
Diphenhydramine is excreted mainly in the urine with very little excreted as unchanged drug.

5.3 Pre-clinical Safety Data

Dextromethorphan
A 13 weeks dietary study in rats has shown no evidence of toxicity at the 0.1mg/kg dextromethorphan level. Dextromethorphan has been reported to have no mutagenic potential in two species and no effect on perinatal or postnatal mortality in high doses.

Diphenhydramine
In the rat, administration of 12mg/kg i.p. diphenhydramine hydrochloride has been reported to produce foetal mortality and mortality in the offspring up to the tenth day after birth. Doses up to 20 and 25 times the human dose (on a mg/kg basis) exert no teratogenic effects in rats and rabbits.

There is no evidence for diphenydramine being mutagenic or carcinogenic in man.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Benzoate (E211)
Ethanol (96%)
Hydroxyethylcellulose (Natrosol G PH)
Povidone K30
Glycerol (E422)
Liquid Sorbitol Non-Crystallising (E420)

Liquid Maltitol (Contains Maltitol (E965) and Sorbitol (E420))
Saccharin Sodium
Capsicum Tincture (Contains Ethanol)
Menthol
Peppermint Oil
Anise Oil
Citric Acid Monohydrate
Macrogol Cetostearyl Ether
Caramel
Blackcurrant Flavour 1122267 (Contains Propylene glycol (E1520))

6.2 Incompatibilities

None

6.3 Shelf-Life

36 months

6.4 Special Precautions for Storage

Store below 25ºC. Protect from light.

6.5 Nature and contents of container

150ml amber soda glass bottle with 28mm tamper evident child resistant closure with EPE/ Saranex liner.

6.6 Special precautions for disposal

Not applicable

7 MARKETING AUTHORISATION HOLDER

Thornton & Ross Ltd
Linthwaite Laboratories
Huddersfield
HD7 5QH

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PL 00240/0042

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