

**THORNTON & ROSS NIGHT TIME ORAL COUGH SYRUP  
PL 00240/0364**

**UKPAR**

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**THORNTON & ROSS NIGHT TIME ORAL COUGH SYRUP  
PL 00240/0364**

**LAY SUMMARY**

The MHRA granted Thornton & Ross Limited a Marketing Authorisation (licence) for the medicinal product Thornton & Ross Night Time Oral Cough Syrup on 26<sup>th</sup> August 2010. This product is indicated for the night time symptomatic relief of unproductive cough and congestive symptoms associated with colds.

This product is available to the general public (supplied through pharmacies only). This product contains dextromethorphan which reduces the desire to cough and diphenhydramine (an antihistamine) which dries up your runny nose and relieves congestion.

No new or unexpected safety concerns arose from this simple application and it was, therefore, judged that the benefits of taking Thornton & Ross Night Time Oral Cough Syrup outweigh the risks; hence a Marketing Authorisation has been granted.

**THORNTON & ROSS NIGHT TIME ORAL COUGH SYRUP  
PL 00240/0364**

**SCIENTIFIC DISCUSSION**

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## **INTRODUCTION**

The UK granted Thornton & Ross Limited a Marketing Authorisation for the medicinal product Thornton & Ross Night Time Oral Cough Syrup (PL 00240/0364) on 26<sup>th</sup> August 2010. The product is available on a Pharmacy Licence (P). This product contains the active ingredients dextromethorphan hydrobromide and diphenhydramine hydrochloride. This product is indicated for the symptomatic relief of coughs.

The application was submitted as a simple abridged application according to Article 10c of Directive 2001/83/EC, cross-referring to Covonia Night Time Formula (PL 00240/0042), which was originally approved to Thornton & Ross Limited on 23<sup>rd</sup> September 1997.

No new data were submitted nor were they necessary for this simple application, as the data are identical to that of the previously granted reference product.

It is considered that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Thornton & Ross Night Time Oral Cough Syrup outweigh the risks; hence a Marketing Authorisation has been granted.

## PHARMACEUTICAL ASSESSMENT

**LICENCE NO:** PL 00240/0364  
**PROPRIETARY NAME:** Thornton & Ross Night Time Oral Cough Syrup  
**ACTIVE(S):** Dextromethorphan hydrobromide and diphenhydramine hydrochloride  
**COMPANY NAME:** Thornton & Ross Limited  
**E.C. ARTICLE:** Article 10c of Directive 2001/83/EC  
**LEGAL STATUS:** P

### 1. INTRODUCTION

This is a simple, piggy back application for Thornton & Ross Night Time Oral Cough Syrup (PL 00240/0364) submitted under Article 10c of Directive 2001/83/EC. The proposed MA holder is Thornton & Ross Limited, Linthwaite Laboratories, Huddersfield, HD7 5QH, United Kingdom.

The application cross-refers to Covonia Night Time Formula (PL 00240/0042), which was originally approved to Thornton & Ross Limited on 23<sup>rd</sup> September 1997.

The current application is considered valid.

### 2. MARKETING AUTHORISATION APPLICATION FORM

#### 2.1 Name(s)

The proposed name of the product is Thornton & Ross Night Time Oral Cough Syrup. The product has been named in-line with current requirements.

#### 2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

The product contains dextromethorphan hydrobromide and diphenhydramine hydrochloride, equivalent to 6.65mg/5ml and 10.0/5ml. The finished product is packaged in 150ml amber soda glass bottles, sealed with 28mm child resistant closure with an expanded polyethylene (EPE)/Saranex liner.

The proposed shelf-life is 36 months for an unopened product with storage conditions are 'Do not store above 25°C' and 'Protect from light'. The shelf-life and storage conditions are consistent with the details registered for the cross-reference product.

#### 2.3 Legal status

On approval, the product will be available on a Pharmacy licence (P).

#### 2.4 Marketing authorisation holder/Contact Persons/Company

Thornton & Ross Limited, Linthwaite Laboratories, Huddersfield, HD7 5QH, United Kingdom.

The QP responsible for pharmacovigilance is stated and his CV is included.

#### 2.5 Manufacturers

The proposed manufacturing sites are consistent with those registered for the cross-reference product and evidence of GMP compliance has been provided.

**2.6 Qualitative and quantitative composition**

The proposed composition is consistent with the details registered for the cross-reference product.

**2.7 Manufacturing process**

The proposed manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch size for each product is stated.

**2.8 Finished product/shelf-life specification**

The proposed finished product specification is in-line with the details registered for the cross-reference product.

**2.9 Drug substance specification**

The proposed drug substance specification is consistent with the details registered for the cross-reference product.

**2.10 TSE Compliance**

None of the excipients used contain material of animal or human origin.  
This is consistent with the cross-reference product.

**3. EXPERT REPORTS**

The applicant has included detailed expert reports in Module 2 of the application. Signed declarations and copies of the experts' CVs are enclosed in Module 1.4 for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

**4. PRODUCT NAME & APPEARANCE**

See 2.1 for details of the proposed product name. The appearance of the product is identical to the cross-reference product.

**5. SUMMARY OF PRODUCT CHARACTERISTICS**

The proposed summary is consistent with the details registered for the cross-reference product.

**6. PATIENT INFORMATION LEAFLET/CARTON****PIL**

The patient information leaflet has been prepared in-line with the details registered for the cross-reference product. The package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that they contain.

Labelling

The proposed artwork is comparable to the artwork registered for the cross-reference product and complies with statutory requirements. In-line with current legislation, the applicant has also included the name of the product in Braille on the packaging and has included sufficient space for a standard UK pharmacy dispensing label.

**7. CONCLUSIONS**

The data submitted with the application is acceptable. The grant of a Marketing Authorisation is recommended.

**PRECLINICAL ASSESSMENT**

No new preclinical data have been supplied with this application and none are required for an application of this type.

The applicant has provided adequate justification for the absence of an Environmental Risk Assessment.

**CLINICAL ASSESSMENT**

No new clinical data have been supplied with this application and none are required for an application of this type.

## **OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT**

### **QUALITY**

The data for this application is consistent with that previously assessed for the cross-reference product and, as such, has been judged to be satisfactory.

### **PRECLINICAL**

No new preclinical data were submitted and none are required for an application of this type.

### **EFFICACY**

This application is identical to a previously granted application for Covonia Night Time Formula (PL 00240/0042), which was originally approved to Thornton & Ross Limited on 23<sup>rd</sup> September 1997.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

### **RISK BENEFIT ASSESSMENT**

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's product is identical to the cross-reference product. Extensive clinical experience with dextromethorphan hydrobromide and diphenhydramine hydrochloride is considered to have demonstrated the therapeutic value of the compounds. The risk:benefit is, therefore, considered to be positive.

**THORNTON & ROSS NIGHT TIME ORAL COUGH SYRUP  
PL 00240/0364**

**STEPS TAKEN FOR ASSESMENT**

1	The MHRA received the Marketing Authorisation application on 8 <sup>th</sup> February 2010.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 17 <sup>th</sup> February 2010.
3	Following assessment of the application, the MHRA requested further information relating to the quality dossier on 25 <sup>th</sup> May 2010 and 21 <sup>st</sup> July 2010.
4	The applicant responded to the MHRA's requests, providing further information on 29 <sup>th</sup> June 2010 and 4 <sup>th</sup> August 2010 for the quality section.
5	The application was determined on 26 <sup>th</sup> August 2010.

**THORNTON & ROSS NIGHT TIME ORAL COUGH SYRUP  
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**STEPS TAKEN AFTER ASSESSMENT**

<b>Date submitted</b>	<b>Application type</b>	<b>Scope</b>	<b>Outcome</b>

**SUMMARY OF PRODUCT CHARACTERISTICS****1 NAME OF THE MEDICINAL PRODUCT**

Thornton & Ross Night Time Oral Cough Syrup

**2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Dextromethorphan Hydrobromide Ph.Eur. 6.65mg/5ml dose.

Diphenhydramine Hydrochloride Ph.Eur. 10.0mg/5ml dose.

Excipients: Each 5ml contains Liquid Maltitol 1.125g, Ethanol (Alcohol) 7.3 vol %

For a full list of excipients see section 6.1

**3 PHARMACEUTICAL FORM**

Oral Syrup

**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***PosologyAdults, the Elderly and Children over 12 years

3 x 5ml spoonfuls at bedtime. Repeat after 6 hours if required.

Children under 12 years

Not recommended.

**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.

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

This medicinal product should not be used in patients with liver dysfunction. It should not be administered to patients where cough is associated with asthma or patients with productive cough.

**4.4 *Special warnings and precautions for use***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.

Patients with rare hereditary problems of fructose intolerance should not take this medicine.

It also contains 7.3vol % ethanol (alcohol), i.e. up to 870mg per dose, equivalent to 22ml of beer or 9ml of wine per dose.

Harmful if suffering from alcoholism.

Special warnings

If symptoms persist consult your doctor.

Keep out of the reach and sight of children.

Do not exceed the stated dose.

Causes drowsiness which may continue the next day. If affected to not drive or operate machinery.

Avoid alcoholic drink.

**4.5 *Interaction with other medicinal products and other forms of interaction***

Dextromethorphan 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 a severe or fatal interaction. Cimetidine inhibits the metabolism of opioid analgesics.

Diphenhydramine has additive sedative effects with alcohol and other CNS depressants. It may also have additive antimuscarinic effects with antimuscarinic drugs.

**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. This medicinal product 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.

**4.8 *Undesirable effects***

Side-effects are uncommon with dextromethorphan. Rarely, drowsiness, nausea, vomiting, dizziness and gastro-intestinal disturbances may occur.

The most common effects of diphenhydramine are drowsiness and a lowered ability to concentrate. Other effects include dizziness, nausea, nervousness, ataxia, abnormal vision, tremor and vomiting. Antimuscarinic effects may include dry mouth, thickened mucous secretions, palpitations and urinary tract dysfunction. Administration of antihistamines has also been associated with rash, angioedema, convulsions and paresthesias.

**4.9 *Overdose***

Acute overdose of dextromethorphan does not usually result in serious signs and symptoms unless very large amounts have been ingested. Signs and symptoms of substantial overdose may include nausea and vomiting, CNS disturbances (hyperexcitability, irritability, mental confusion, lethargy, somnolence, ataxia, auditory and visual hallucinations), nystagmus and respiratory depression.

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. 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: R05DA – 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 ethanalamine H<sub>1</sub> 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 is extensively metabolised in the liver. It is mainly metabolised to dextrophan by O-demethylation involving the cytochrome P45011D6 isozyme, which is then conjugated by UDP-glucuronosyl transferases. Up to 9% of individuals have been found to be poor metabolisers and the half-life of dextromethorphan may be extremely prolonged in these people.

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.

Oriental 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 didesmethylidiphenhydramine. 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 *Preclinical 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 diphenhydramine being mutagenic or carcinogenic in man.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 *List of excipients***

Sodium Benzoate

Ethanol (96%)

Hydroxyethylcellulose. (Natrosol G PH).

Povidone K30.

Glycerol.

Liquid Sorbitol Non-Crystallising.

Liquid Maltitol

Saccharin Sodium.

Capsicum Tincture.

Menthol.

Peppermint Oil.

Anise Oil.

Citric Acid Monohydrate.

Macrogol Cetostearyl Ether

Caramel.

Blackcurrant Flavour 1122267 – containing propylene glycol.

Purified Water.

- 6.2**     *Incompatibilities*  
None.
- 6.3**     *Shelf life*  
36 months.
- 6.4**     *Special precautions for storage*  
Store below 25°C. Protect from light.
- 6.5**     *Nature and contents of container*  
150ml amber soda glass bottles with 28mm child resistant closure with EPE/Saranex liner.
- 6.6**     *Special precautions for disposal*  
Any unused product or waste material should be disposed of in accordance with local requirements.
- 7**       **MARKETING AUTHORISATION HOLDER**  
Thornton & Ross Ltd.  
Linthwaite Laboratories  
Huddersfield  
HD7 5QH.
- 8**       **MARKETING AUTHORISATION NUMBER(S)**  
PL: 00240/0364
- 9**       **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**  
26/08/2010
- 10**     **DATE OF REVISION OF THE TEXT**  
26/08/2010

Thornton & Ross Night Time Oral Cough Syrup contains dextromethorphan which reduces the desire to cough and diphenhydramine (an antihistamine) which dries up your runny nose and relieves congestion.

### 1. Before you use this medicine

#### ■ Do not use the medicine if you have....

- An **allergy** to any of the ingredients listed in section 3
- Taken **MAOIs (monoamine oxidase inhibitors)** for depression within the last two weeks
- **Shortage of breath** • **Liver problems** • **Asthma** or a **cough** which produces **phlegm**.

#### ■ Talk to your doctor if you have....

- Glaucoma. • Difficulty passing urine • Prostate trouble
- A blocked intestine • Epilepsy • Heart problems

#### ■ Talk to your doctor or pharmacist if you are taking....

- Alcohol • Cimetidine for stomach ulcers • Other drugs which make you drowsy • Medicine for a runny nose or to control the bladder.

#### ■ Driving and using machines....

This medicine causes drowsiness and you should not drive or operate machinery until the effects have worn off.

#### ■ Pregnant or breastfeeding....

Ask your doctor or pharmacist for advice before using if you are pregnant, might be pregnant or are breastfeeding. This medicine should not be used unless the doctor has told you to do so.

#### ■ Important ingredient information

- Contains maltitol liquid and sorbitol. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine
- It contains 7.3vol% of ethanol (alcohol), i.e. up to 870mg per dose, equivalent to 22ml of beer or 9ml of wine per dose. Harmful for those suffering from alcoholism. To be taken into account in children and high risk groups such as patients with liver disease or epilepsy.

M691

### 2. Possible side effects

Like all medicines, Thornton & Ross Night Time Oral Cough Syrup can have side effects, although these don't affect everyone.

**Important side effects.** If you get any of these side effects stop use immediately and see a doctor as soon as possible: • swelling of the lips, mouth, eyes or tongue • fits.

**Other possible side effects:** drowsiness and lack of concentration • dizziness • muscle twitching • trembling • nervousness • blurred vision • sickness or feeling sick • rash • skin blisters • pins and needles • dry mouth • thick saliva • palpitations • difficulty passing urine • stomach upsets. If you notice these or any other side effects not listed, stop use and tell your doctor or pharmacist.

### 3. Further information

■ **If you accidentally take too much** see a doctor straight away. Take the pack with you to show which medicine you have swallowed.


- Do not use after the expiry date. The expiry date refers to the last day of that month.
- Return any unused medicine to the pharmacy for disposal.

**The active ingredients per 5ml are:** dextromethorphan hydrobromide 6.65mg, diphenhydramine hydrochloride 10mg. **The other ingredients are:** ethanol, glycerol (E422), sorbitol (E420), sodium benzoate, maltitol liquid, hydroxyethylcellulose, povidone (E1202), saccharin sodium, capsicum tincture (capsicum oleoresin), menthol, peppermint oil, anise oil, citric acid (E330), macrogol cetostearyl ether, caramel (E150), blackcurrant flavour (containing propylene glycol) and purified water.

#### What the medicine looks like

Thornton & Ross Night Time Oral Cough Syrup is a brown syrupy liquid. It is supplied in 150ml bottles.

**This label was revised in June 2010** M691


**IMPORTANT: Peel top leaf and read all text inside BEFORE use. Do not tear off, re-fix for future use.** **Peel Here** 

**Thornton & Ross Night Time Oral Cough Syrup** is for night time relief of the symptoms of dry coughs and congestion from colds.  
**SHAKE THE BOTTLE.**  
Take the solution by mouth.  
**Adults, the elderly and children over 12 years:**  
Take 3 x 5ml spoonfuls at bedtime. Repeat after 6 hours if required.  
**Do not give to children under 12 years old.**  
**DO NOT EXCEED THE STATED DOSE.**  
If symptoms persist consult your doctor.


**Warning: causes drowsiness which may continue the next day. If affected do not drive or operate machinery. Avoid alcoholic drink.**

Do not store above 25°C. Protect from light.  
**Keep out of the reach and sight of children.**  
**Active ingredients per 5ml:** dextromethorphan hydrobromide 6.65mg, diphenhydramine hydrochloride 10mg. **Also contains:** ethanol, glycerol (E422), sorbitol (E420), sodium benzoate, maltitol liquid, propylene glycol. Alcohol 7.3 vol%. **See reverse for full list.**

**MA holder and manufacturer**  
Thornton and Ross Ltd.,  
Huddersfield,  
HD7 5QH, UK  
PL 00240/0042  
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**Overprint Area**

COVONIA is a registered Trade Mark.  
**P**  
150ml e 

*Thornton & Ross*  
**NIGHT TIME**  
**Oral Cough**  
*Syrup*

Dextromethorphan Hydrobromide  
Diphenhydramine Hydrochloride

Calms and controls  
troublesome coughs  
and so aids restful sleep

**DRY NIGHT TIME COUGHS**

M692

**ONLY FOR USE AT  
NIGHT TIME**

*Thornton & Ross*  
**NIGHT TIME**  
**Oral Cough**  
*Syrup*

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M692

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