DEXTROMETHORPHAN HYDROBROMIDE 10MG/5ML ORAL SOLUTION

PL 17907/0314

UKPAR

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DEXTROMETHORPHAN HYDROBROMIDE 10MG/5ML ORAL SOLUTION

PL 17907/0314

LAY SUMMARY

On 26 January 2012, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Bristol Laboratories Limited a Marketing Authorisation (licence) for the medicinal product Dextromethorphan Hydrobromide 10mg/5ml Oral Solution (PL 17907/0314). This is a pharmacy (P) medicine used to relieve dry and tickly coughs.

This medicine contains dextromethorphan hydrobromide as the active ingredient, which acts as a cough suppressant and helps to reduce coughing.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Dextromethorphan Hydrobromide 10mg/5ml Oral Solution outweigh the risks; hence a Marketing Authorisation has been granted.

DEXTROMETHORPHAN HYDROBROMIDE 10MG/5ML ORAL SOLUTION

PL 17907/0314

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Bristol Laboratories Limited a Marketing Authorisation for the medicinal product Dextromethorphan Hydrobromide 10mg/5ml Oral Solution (PL 17907/0314) on 26 January 2012. This is a pharmacy (P) medicine for the relief of persistent dry irritant coughs.

This application was submitted according to Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing an active substance of well-established use.

Dextromethorphan Hydrobromide 10mg/5ml Oral Solution contains the active ingredient dextromethorphan hydrobromide. Dextromethorphan hydrobromide is a cough suppressant, which has a central action on the cough centre in the medulla. It has no analgesic properties and little sedative activity.

No new non-clinical or clinical studies were conducted for this application, which is acceptable given that this is a bibliographic application for a product containing an active of well-established use.

No new or unexpected safety concerns were raised during the assessment of this application and it was, therefore, judged that the benefits of taking Dextromethorphan Hydrobromide 10mg/5ml Oral Solution outweigh the risks; hence a Marketing Authorisation has been granted.

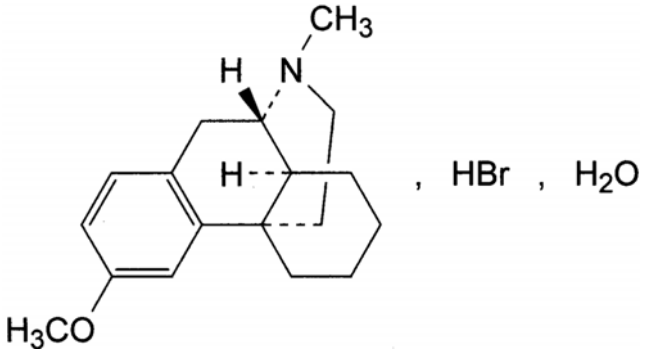
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE:

INN: Dextromethorphan hydrobromide

Chemical name: ent-3-methoxy-17-methylmorphinan hydrobromide monohydrate.

Structure:



Molecular formula: $C_{18}H_{26}BrNO, H_2O$

Molecular weight 370.3

Appearance: Almost white, crystalline powder.

Solubility: Dextromethorphan hydrobromide is sparingly soluble in water, freely soluble in alcohol.

Dextromethorphan hydrobromide is the subject of a European Pharmacopoeia monograph.

The manufacture and control of dextromethorphan hydrobromide is covered by European Directorate for the Quality of Medicines (EDQM) Certificates of Suitability.

MEDICINAL PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients, namely sodium benzoate, anhydrous citric acid, liquid maltitol, saccharin sodium, propylene glycol, strawberry flavour (containing propylene glycol and alpha-tocopherol), contramarum flavouring (containing propylene glycol and benzyl alcohol) and amaranth (E123).

All excipients comply with their respective European Pharmacopoeia monograph with the exception of strawberry flavour, contramarum flavouring and amaranth which comply with suitable in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Pharmaceutical Development

The objective of the development programme was to formulate a safe, efficacious, stable product containing the active ingredient dextromethorphan hydrobromide 10mg/5ml.

Suitable pharmaceutical development data has been provided for this application.

Manufacturing Process
A description and flow-chart of the manufacturing method have been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation data on pilot-scale batches has been provided.

Finished Product Specification
The finished product specification proposed is satisfactory. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications.

Container Closure System
The finished product is packaged in amber-coloured polyethylene terephthalate (PET) bottles, closed by a child-resistant high density polyethylene (HDPE) white-coloured closure along with 1.25, 2.5 and 5 ml polypropylene doubled spoon with EC mark and is available in pack sizes of 150 ml.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability of the Product
Stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 36 months, with the storage conditions, “Do not store above 25°C. Store in the original container. Keep container tightly closed.”

Bioequivalence/Bioavailability
A bioequivalence study was not necessary to support this application.

Summary of Product Characteristics (SmPC), Product Information Leaflets (PILs) and Labelling
The SmPC, PIL and labelling are satisfactory.

A 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, as amended. 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 it contains.

MAA Form
The MAA form is satisfactory.

Expert Report
The pharmaceutical expert report is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.

NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY

No new non-clinical data were submitted, which is acceptable given that this is a bibliographic application for a product containing an active substance of well-established use.

NON-CLINICAL EXPERT REPORT

The non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the non-clinical aspects of the dossier.

CONCLUSION

The grant of a Marketing Authorisation is recommended.

CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
The clinical pharmacology of dextromethorphan hydrobromide is well-known. No new pharmacodynamic or pharmacokinetic data are provided or required for this application.

EFFICACY
No new efficacy data were submitted or required for this application.

SAFETY
No new safety data were submitted or required for this application. The applicant has provided an acceptable safety review from the literature. No new safety issues have been raised from this application.

PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN
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 either in the Community or in a third country.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC), PRODUCT FORMATION LEAFLETs (PILs) AND LABELS
The SmPC, PIL and labels are acceptable.

CLINICAL EXPERT REPORT
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

CONCLUSION
The grant of a Marketing Authorisation is recommended.

OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Dextromethorphan Hydrobromide 10mg/5ml Oral Solution are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none were required for this type of application. A non-clinical overview has been provided by an appropriately qualified person and consists of a review of the published literature.

EFFICACY

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

The efficacy of the active is well described and no new studies have been conducted. The applicant has summarised the current state of knowledge in their literature review.

SAFETY

The safety profiles of dextromethorphan hydrobromide are well-known. The literature review identified no new or unexpected safety issues or concerns

PRODUCT LITERATURE

The approved SmPC is satisfactory. The PIL and labelling are satisfactory, and consistent with the approved SmPC.

BENEFIT-RISK ASSESSMENT

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Dextromethorphan hydrobromide is a well-known active substance. Extensive clinical experience with dextromethorphan hydrobromide is considered to have demonstrated the therapeutic value of the product. The benefit-risk is, therefore, considered to be positive.

DEXTROMETHORPHAN HYDROBROMIDE 10MG/5ML ORAL SOLUTION

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STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the marketing authorisation application on 01 July 2009.

2 Following standard checks and communication with the applicant the MHRA considered the application valid on 08 September 2009.

3 Following assessment of the application the MHRA requested further information on the pharmaceutical dossier on 16 October 2009 and 13 April 2011, and further information on the clinical dossier on 23 October 2009.

4 The applicant responded to the MHRA's requests, providing further information on the pharmaceutical dossier on 08 February 2011 and 24 January 2012, and more information on the clinical dossier on 08 February 2011.

5 The application was determined and granted on 26 January 2012.

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Dextromethorphan Hydrobromide 10mg/5ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient
Each 5ml contains
Dextromethorphan Hydrobromide Ph Eur 10mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

A limpid red solution for oral administration.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the relief of persistent dry irritant coughs.

4.2 Posology and method of administration

For oral administration.

Adults and children over 12: Take 10-20mg every 4-6 hours (1-2 spoonful of 5ml), up to a maximum of 80 mg/day. Do not exceed the 4 daily intakes.

Children between 6 and 12 years old: 5-10mg every 4-6 hours (1 spoonful of 2.5ml to 1 spoonful of 5ml), up to a maximum of 40 mg/day. Do not exceed the 4 daily intakes.

Children of 6-12 years of age: not to be used for more than 5 days without the advice of a doctor. Parents and carers should seek medical attention if the child's condition deteriorates during treatment.

Keep out of the sight and reach of children.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Liver disease, exacerbation of asthma.

Dextromethorphan should not be given to patients in, or at risk of developing respiratory failure (for example during an acute asthma attack or in patients with Chronic Obstructive Pulmonary Disease).

Patients taking monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping such treatment (see section 4.5).

Patient taking serotonin reuptake inhibitors (SSRIs, see section 4.5)

Not to be used in children under 6 years.

4.4 Special warnings and precautions for use

Patients suffering from chronic cough, asthma or patients suffering from an acute asthma attack should be a consult a Healthcare Professional before use.

Do not prescribe this product outside the recommended dose. (see section 4.2)

Use with caution in patients with hepatic dysfunction.

Not to be taken with any other cough and cold medicine.

Use of Dextromethorphan with alcohol or other CNS depressants may increase the effects on the CNS and cause toxicity in relatively smaller doses.

Should be used with caution in atopic children due to histamine release.

Dextromethorphan Hydrobromide 10mg/5ml Oral Solution contains Liquid Maltitol Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Not to be used in patients taking monoamine inhibitors or within 14 days of stopping treatment as there is a risk of serotonin syndrome (pyrexia, hypertension, arrhythmias) when MOAI are taken in combination with dextromethorphan.

Dextromethorphan is primary metabolised by the cytochrome P450 isoenzyme CYP 2D6; there is a possibility of interactions with inhibitors of this enzymes, including amiodarone, haloperidol, propafenone, quinidine, SSRIs and thioridazine. For example, Quinidine and amiodarone can increase serum concentrations of dextromethorphan markedly and some patients have experienced symptoms of dextromethorphan toxicity when the two agents have been used together.

Dextromethorphan might exhibit additive CNS depressant effects when co-administered with alcohol, antihistamines, psychotropics and other CNS depressants.

4.6 Pregnancy and lactation

Although dextromethorphan has been in widespread use for many years without apparent illconsequence, there are no specific data on its use during pregnancy. Caution should therefore be exercised by balancing the potential benefit of treatment against any possible hazards. It is not known whether dextromethorphan or its metabolites are excreted in human milk.

4.7 Effects on ability to drive and use machines

Dextromethorphan Hydrobromide may cause drowsiness and dizziness. Patients affected should not drive or operate machinery.

4.8 Undesirable effects

Gastrointestinal Disorders
Rare: Gastrointestinal upset (nausea, vomiting,and diarrhoea)

Nervous System Disorders
Rare: Dizziness Drowsiness, excitation, mental confusion, convulsions, respiratory depression, may occur very rarely under normal conditions of use or after overdosage

Hypersensitivity
Rare:Skin reactions including rash.

4.9 Overdose

Symptoms:

These include nausea and vomiting, CNS depression, dizziness, dysarthria (slurred speech), nystagmus, somnolence (drowsiness), excitation, mental confusion, psychotic disorder (psychosis), and respiratory depression.

Management:

Treatment of overdose should be symptomatic and supportive. Gastric lavage may be of use. Naloxone has been used successfully as a specific antagonist to dextromethorphan toxicity in children.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cough suppressant
ATC code: R05DA09

Dextromethorphan hydrobromide is a cough suppressant which has a central action on the cough centre in the medulla. It has no analgesic properties and little sedative activity.

5.2 Pharmacokinetic properties

Dextromethorphan hydrobromide is well absorbed from the gastrointestinal tract. It is metabolised in the liver and excreted in the urine as unchanged dextromethorphan and demethylated metabolites including dextrorphan, which has some cough suppressant activity.

5.3 Preclinical safety data

There is no relevant information additional to that already contained elsewhere in the SPC or of relevance to the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Benzoate
Anhydrous citric acid
Liquid maltitol
Saccharin sodium
Propylene glycol
Strawberry flavour (containing propylene glycol and alpha-tocopherol)
Contramarum flavouring (containing propylene glycol and benzyl alcohol)
Amaranth (E123)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original container. Keep the container tightly closed.

6.5 Nature and contents of container

Dextromethorphan Hydrobromide 10mg/5ml oral solution is packed into amber coloured polyethylene terephthalate (PET) bottle, closed by a child-resistant high density polyethylene (HDPE) white coloured closure along with 1.25, 2.5 and 5 ml polypropylene doubled spoon with EC mark.

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

BRISTOL LABORATORIES LIMITED
Unit 3, Canalside, Northbridge Road
Berkhamsted, Hertfordshire,
HP4 1EG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 17907/0314

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/01/2012

10 DATE OF REVISION OF THE TEXT

26/01/2012

PRODUCT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR USER

Dextromethorphan Hydrobromide 10mg/5ml Oral Solution

Dextromethorphan Hydrobromide

Read all of this leaflet carefully before you start taking this medicine.

This medicine is available without prescription; however you still need to take it carefully to get the best results from it.

- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- You must contact a doctor if your symptoms worsen or do not improve.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1.WHAT DEXTROMETHORPHAN HYDROBROMIDE 10mg/5ml ORAL SOLUTION IS AND WHAT IT IS USED FOR

Dextromethorphan Hydrobromide acts as a cough suppressant which acts to reduce coughing.
It can be used to relieve dry and tickly coughs. Dry coughs do not produce phlegm or mucus on the chest.
For children, simple treatments should be tried first before you give this medicine.

2.BEFORE YOU TAKE DEXTROMETHORPHAN HYDROBROMIDE 10mg/5ml

Do not take this medicine if you:

- are allergic to this medicine or any of the other ingredient (these are listed in Section 6, Further Information)
- have liver problems
- have difficulty in breathing
- You are taking any of the following or have within the last two weeks taken monoamine oxidase inhibitors or SSRIs (both are types of anti-depressants) and if you are uncertain as to whether you are taking such medication, talk to your doctor or pharmacist.

Take special care with this medicine if you:

- have long term cough or asthma (do not take this medicine if you are wheezing or if you are having an asthma attack)
- have cough which produces lots of phlegm
- are treating a child who is prone to allergies

Talk to your doctor or pharmacist for advise

Taking other medicines:

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed, for example, herbal remedies and health supplements from a pharmacy, supermarket or health food shop, as they may interact with this medicine.

Examples of medicines which can affect to this medicine are:

- medicines for allergies
- sedatives or other medicines that make you feel sleepy
- medicines for mental health conditions
- medicines for heart problems

Pregnancy and breast-feeding

- Do not take this medicine if you are pregnant or breast-feeding

Driving and using machines

This medicine may make you feel dizzy and drowsy.
Do not drive or use machines until you are sure you are not affected.

Taking this medicine with alcohol

Do not drink alcohol whilst taking this medicine. Alcohol increases the risk of side effects occurring and may make you feel more drowsy.

Important information about some of the other ingredients of the solution

This medicine contains **Maltitol.** If you have been previously told by your doctor you have fructose intolerance, contact your doctor before taking this medicine.

3.HOW TO TAKE DEXTROMETHORPHAN HYDROBROMIDE 10mg/5ml ORAL SOLUTION

You should check with your doctor or pharmacist if you are not sure.
The usual doses are as follows:
Adults and children over 12: Take 10-20mg every 4-6 hours (1-2 spoonful of 5ml), up to a maximum of 80mg/day.
Do not exceed the 4 daily intakes.

Children between 6 and 12 years old: 5-10mg every 4-6 hours (1 spoonful of 2.5ml to 1 spoonful of 5ml), up to a maximum of 40mg/day. Do not exceed the 4 daily intakes.

For children of 6-12 years of age do not use for more than 5 days without the advice of a doctor. Parents and carers should seek medical attention if the child's condition deteriorates during treatment.

Do not give to Children under 6 years of age.

If you take more medicine than you should

If you accidently take too much Dextromethorphan Hydrobromide 10mg/5ml oral solution, tell your doctor immediately or contact your nearest Hospital Casualty/Accident and Emergency Department even if there are no signs of discomfort.
Take this medication in its original packaging with you in order to enable the doctor to identify your medication easily.

If you forget to take the medicine

If you forget to take a dose, take it as soon as you remember. Then carry on as before, but do not take double dose to make up for forgotten dose.

4.POSSIBLE SIDE EFFECTS

Like all medicines Dextromethorphan Hydrobromide 10mg/5ml Oral Solution can cause side effects, although not everyone will get them.

- Skin reactions such as skin rash
- Feeling sick, being sick, diarrhoea
- Feeling drowsy, dizzy, excited or confused
- Fits
- Breathing problems

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE DEXTROMETHORPHAN HYDROBROMIDE 10mg/5ml ORAL SOLUTION

- Keep this medicine in a safe place where children cannot see or reach it.
- Do not store above 25°C. Store in the original container. Keep the container tightly closed.
- Do not use this medicine after the expiry date printed on the pack. The expiry date refers to the last day of that month.
- Do not use this medicine if you notice any visible signs of deterioration.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Dextromethorphan Hydrobromide 10mg/5ml Oral Solution contains

- The active substance in Dextromethorphan Hydrobromide 10mg/5ml Oral Solution is Dextromethorphan Hydrobromide.
- Each 5ml of Dextromethorphan Hydrobromide 10mg/5ml Oral Solution contains 10mg of Dextromethorphan Hydrobromide.

Other ingredients are Sodium Benzoate, Anhydrous citric acid, Liquid maltitol, Saccharin sodium, Propylene glycol, Strawberry flavour (containing propylene glycol and alpha-tocopherol), Contramarum flavouring (containing propylene glycol and benzyl alcohol), (Amaranth) E123.

What Dextromethorphan Hydrobromide 10mg/5ml Oral Solution looks like and contents of the pack

- A limpid red solution for oral administration.
- Dextromethorphan Hydrobromide 10mg/5ml oral solution is packed into amber coloured polyethylene terephthalate (PET) bottle, closed by a high density polyethylene (HDPE) white coloured closure. 1.25, 2.5 and 5 ml polypropylene doubled spoon with EC mark are provided as administration device.

Marketing Authorisation Holder

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Dextromethorphan Hydrobromide 10mg/5ml Oral Solution: PL 17907/0314

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LABELLING

Carton:

Bottle label: