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DICYCLOVERINE ORAL SOLUTION
PL 20620/0010

LAY SUMMARY

On 18th May 2009, the MHRA granted NRIM Limited a Marketing Authorisation (licence) for Dicycloverine Oral Solution.

Dicycloverine Oral Solution contains the active ingredient dicycloverine hydrochloride, which belongs to a group of medicines called anticholinergic antispasmodics. These drugs are commonly used to relieve painful bowel cramps. Their anticholinergic action helps to relax the muscle of the intestines and relieve the intestines.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Dicycloverine Oral Solution outweigh the risks, hence a Marketing Authorisation has been granted.
DICYCLOVERINE ORAL SOLUTION
PL 20620/0010

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product Dicycloverine Oral Solution (PL 20620/0010) to NRIM Limited on 18th May 2009. The product is a prescription-only medicine containing dicycloverine hydrochloride. Dicycloverine hydrochloride is a smooth muscle antispasmodic, primarily indicated for treatment of functional conditions involving smooth muscle spasm of the gastrointestinal tract. The commonest of these are irritable colon (mucous colitis, spastic colon).

This application for Dicycloverine Oral Solution is submitted as an abridged application according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal product to Merbentyl Syrup (Aventis Pharma Limited), which was first licensed in the UK in July 1983.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Dicycloverine hydrochloride

INN: Dicycloverine hydrochloride, Dicyclomine hydrochloride
Chemical name: [Bicyclohexyl]-1-Carboxylic acid, 2-(Diethylamino) ethyl ester, hydrochloride
2-(Diethylamino) ethyl [Bicyclohexyl]-1-Carboxylate, hydrochloride

Structure:

Physical form: A white or almost white, crystalline powder, soluble in water, freely soluble in alcohol and in methylene chloride. It shows polymorphism

Molecular formula: C_{19}H_{35}NO_{2}.HCl
Molecular weight: 345.95

A European pharmacopoeial monograph has been written for active dicycloverine hydrochloride.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance dicycloverine hydrochloride. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analysis data are provided and comply with the proposed specification.

Specifications have been provided for all packaging used. All primary packaging complies with current European Directives concerning contact with food.

A suitable retest period has been determined, based on stability data.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely sodium benzoate, invert syrup, citric acid monohydrate, cherry flavour, raspberry flavour, vanilla flavour and blackcurrant flavour. With the exception of the flavourings and the invert syrup, all excipients used comply with their respective European Pharmacopoeia monograph. Invert syrup complies with the British Pharmacopoeia and the flavourings comply with suitable in-house specifications.
Satisfactory certificates of analysis have been provided for all excipients.

None of the excipients used contain materials of animal or human origin.

**Product development**
The objective of the development programme was to produce a product that could be considered a generic medicinal product of Merbentyl Syrup (Aventis Pharma Limited). The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid.

Comparative impurity data have been provided for the finished product versus the originator product Merbentyl Syrup (Aventis Pharma Limited).

**Manufacture**
A description and flow-chart of the manufacturing method has been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of finished product and the results appear satisfactory.

**Finished product specification**
The finished product specification is satisfactory. Test methods have been described and have been adequately validated as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis for all working standards used have been provided and are satisfactory.

**Container-Closure System**
The primary packaging is a Type III amber glass bottle, with a polyethylene seal and a pilfer-proof closure. Pack size is one bottle containing 120ml syrup.

Specifications and Certificates of Analysis for all packaging have been provided. These are satisfactory. The primary packaging has been shown to comply with relevant regulations regarding the contact of materials with foodstuff.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 24 months has been set, with the storage instructions “Do not store above 25°C. Store in the original container”.

**ADMINISTRATIVE**

**Expert Report**
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

**Summary of Product Characteristics (SPC)**
This is pharmaceutically satisfactory.

**Labelling**
These are pharmaceutically satisfactory.
Patient Information Leaflet (PIL)
This is pharmaceutically 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
This is pharmaceutically satisfactory.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application.
PRECLINICAL ASSESSMENT

This application for Dicycloverine Oral Solution is submitted as an abridged application according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal product of Merbentyl Syrup (Aventis Pharma Limited), which was first authorised in July 1983.

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

CLINICAL PHARMACOLOGY
No new clinical pharmacology data have been submitted with this application. As the product is an oral solution containing active substance in the same concentration as the innovator (and the excipients do not affect gastrointestinal transit, absorption or in vivo stability of the active), no new clinical pharmacology data are required.

EFFICACY
No new data has been provided and none are required for an application of this type.

SAFETY
No new data has been provided and none are required for an application of this type.

EXPERT REPORTS
The clinical expert report has been written by a suitably qualified person and is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)
This is consistent with that for the reference product and is satisfactory.

LABELLING
These are satisfactory

APPLICATION FORM (MAA)
This is satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
This is consistent with that for the reference product and is satisfactory.

DISCUSSION
As this is an oral solution containing the same amounts of active substance as the reference product and similar impurity levels, it can be considered as essentially similar.

MEDICAL CONCLUSION
The grant of a marketing authorisation is recommended for this application.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Dicycloverine 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.

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

EFFICACY
The applicant’s Dicycloverine Oral Solution and the reference product Merbentyl Syrup (Aventis Pharma Limited) can be considered as bioequivalent.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with those for the reference product Merbentyl Syrup (Aventis Pharma Limited).

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. A qualitative and quantitative comparison supports the claim that the applicant’s products and the reference products are interchangeable. Extensive clinical experience with dicycloverine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.
## STEPS TAKEN FOR ASSESSMENT

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<th>Description</th>
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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 30th March 2007</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 31st May 2007</td>
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<td>3</td>
<td>Following assessment of the applications, the MHRA requested further information relating to the quality dossiers on 21st August 2007 and 5th February 2008. No requests for further information were made for the clinical dossiers.</td>
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<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 1st February 2008 and 24th April 2008 for the quality sections.</td>
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<td>5</td>
<td>The applications were determined on 18th May 2009</td>
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### STEPS TAKEN AFTER AUTHORISATION - SUMMARY

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<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
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NAME OF THE MEDICINAL PRODUCT
Dicycloverine Oral Solution

QUALITATIVE AND QUANTITATIVE COMPOSITION
Dicycloverine Hydrochloride 10mg/5ml

PHARMACEUTICAL FORM
Solution

CLINICAL PARTICULARS

4.1 Therapeutic indications
Dicycloverine is a smooth muscle antispasmodic primarily indicated for treatment of functional conditions involving smooth muscle spasm of the gastrointestinal tract. The commonest of these are irritable colon (mucous colitis, spastic colon).

4.2 Posology and method of administration

Adults
One to two 5ml spoonfuls (10 - 20mg) three times daily before or after meals.

Children (2-12 years):
One 5ml spoonful (10mg) three times daily.

Children (6 months - 2 years)
5 - 10mg three or four times daily, 15 minutes before feeds. Do not exceed a daily dose of 40mg. If it is necessary to dilute Dicycloverine Oral Solution this may be done using Syrup or if diluted immediately prior to use with water.

4.3 Contraindications
Known idiosyncrasy to dicycloverine hydrochloride. Infants under 6 months of age.

4.4 Special warnings and precautions for use
Products containing dicycloverine hydrochloride should be used with caution in any patient with or suspected of having glaucoma or prostatic hypertrophy. Use with care in patients with hiatus hernia associated with reflux oesophagitis because anticholinergic drugs may aggravate the condition. There are reports of infants, 3 months of age and under, administered dicycloverine hydrochloride syrup who have evidenced respiratory symptoms (breathing difficulty, shortness of breath, breathlessness, respiratory collapse, apnoea) as well as seizures, syncope, asphyxia, pulse rate fluctuations, muscular hypotonia and coma. The above symptoms have occurred within minutes of ingestion and lasted 20-30 minutes. The symptoms were reported in association with dicycloverine hydrochloride oral solution therapy but the cause and effect relationship has neither been disproved or proved. The timing and nature of the reactions suggest that they were a consequence of local irritation and/or aspiration, rather than to a direct pharmacological effect. Although no causal relationship between these effects, observed in infants and dicycloverine administration has been established, dicycloverine hydrochloride is contra-indicated in infants under 6 months of age.

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
None

4.6 Pregnancy and lactation
Epidemiological studies in pregnant women with products containing dicycloverine hydrochloride (at doses up to 40mg/day) have not shown that dicycloverine hydrochloride increases the risk of foetal abnormalities if administered during the first trimester of pregnancy. Reproduction studies have been performed in rats and rabbits at doses of up to 100 times the maximum recommended dose (based on 60mg per day for an adult person) and have revealed no evidence of impaired fertility or harm to the foetus due to dicycloverine. Since the
risk of teratogenicity cannot be excluded with absolute certainty for any product, the drug should be used during pregnancy only if clearly needed.

It is not known whether dicycloverine is secreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when dicycloverine is administered to a nursing mother.

4.7 Effects on ability to drive and use machines
None

4.8 Undesirable effects
Side-effects seldom occur with Merbentyl. However, in susceptible individuals, dry mouth, thirst and dizziness may occur. On rare occasions, fatigue, sedation, blurred vision, rash, constipation, anorexia, nausea and vomiting, headache and dysuria have also been reported.

4.9 Overdose
Symptoms of Merbentyl overdosage are headache, dizziness, nausea, dry mouth, difficulty in swallowing, dilated pupils and hot dry skin. Treatment may include emetics, gastric lavage and symptomatic therapy if indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Dicycloverine hydrochloride relieves smooth muscle spasm of the gastrointestinal tract.

Animal studies indicate that this action is achieved via a dual mechanism;
(1) a specific anticholinergic effect (antimuscarinic at the ACh-receptor sites) and
(2) a direct effect upon smooth muscle (musculotropic).

5.2 Pharmacokinetic properties
After a single oral 20mg dose of dicycloverine hydrochloride in volunteers, peak plasma concentration reached a mean value of 58ng/ml in 1 to 1.5 hours. 14C labelled studies demonstrated comparable bioavailability from oral and intravenous administration. The principal route of elimination is via the urine.

5.3 Preclinical safety data
Not relevant.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium benzoate
Invert syrup
Citric acid monohydrate
Flavour Cherry – H – 24914
Flavour Raspberry – AF – 2283
Flavour Vanilla – AF – 2268
Flavour Blackcurrant – AF – 2285

6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 months

6.4 Special precautions for storage
Do not store above 25°C. Store in the original container.

6.5 Nature and contents of container
Type III, EP amber glass bottles sealed with a polyethylene screw cap equipped with a polyethylene seal and pilferproof closure.
Pack size: 1 bottle containing 120ml syrup.
6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
NRIM Limited
Marlborough House
298, Regents Park Road
Finchley N3 2UA
London, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 20620/0010

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
18/05/2009

10 DATE OF REVISION OF THE TEXT
18/05/2009
UKPAR Dicycloverine Oral Solution  PL 20620/0010

DICYCLOVERINE 10MG/5ML ORAL SOLUTION
PATIENT INFORMATION LEAFLET

READ ALL OF THIS LEAFLET CAREFULLY BEFORE YOU START USING THIS MEDICINE:
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it onto others. It may harm them, even if their symptoms are the same as yours.
- 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.

THE LEAFLET CONTAINS INFORMATION ON:
1. What Dicycloverine Oral Solution is and what it is used for.
2. Before you take Dicycloverine Oral Solution.
3. How to take Dicycloverine Oral Solution.
4. Possible side effects.
5. How to store Dicycloverine Oral Solution.
6. Further information.

1. WHAT DICYCLOVERINE ORAL SOLUTION IS AND WHAT IT IS USED FOR?
Dicycloverine hydrochloride, the active ingredient of Dicycloverine Oral Solution, is one of a group of medicines called anticholinergic antispasmodics. It is used to relieve painful bladder cramps. The anticholinergic action helps to relax the muscles of the intestine and relieve the painful symptoms.

2. BEFORE YOU TAKE DICYCLOVERINE ORAL SOLUTION
You should not take Dicycloverine Oral Solution unless you are sure it is safe for you to do so.

Do NOT give or take Dicycloverine Oral Solution:
- If you are allergic to dicycloverine hydrochloride or any other ingredients in the products.
- To babies under 4 months old as it may be dangerous for them.

Take special care with Dicycloverine Oral Solution:
Do not take Dicycloverine Oral Solution if:
- You are pregnant or think that you may be pregnant.
- You are breast feeding.
- You have glaucoma (an eye condition involving increased pressure in the eye and resulting in poor vision).
- You have an enlarged prostate gland (this causes difficulty in passing urine).
- You have a history of incontinence with symptoms such as acid and food regurgitation and heartburn.

Taking other medicines:
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines including medicines obtained with no prescription.

Taking Dicycloverine Oral Solution with food or drink:
Dicycloverine Oral Solution may be taken before or after meals.

Pregnancy or breast feeding:
The safety of dicycloverine hydrochloride for use during pregnancy has not been fully established. Hence, it should be taken only if there is a clear need for it.

As it has not been established that dicycloverine does not pass in the breast milk, it should be used with caution in lactating mothers.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines:
The effects of dicycloverine hydrochloride on the ability to drive and operate machinery have been established. Hence do not drive or use machinery when you are on Dicycloverine Oral Solution unless you are sure your judgement and co-ordination are not affected.

Important information about some of the ingredients of Dicycloverine Oral Solution:
Dicycloverine Oral Solution contains invert syrup. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE DICYCLOVERINE ORAL SOLUTION
Always take Dicycloverine Oral Solution exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Adults and children over 12 years old:
One to Two 5ml spoonfuls three times a day. Your doctor will tell you which dose to use.

Children aged 2 - 12 years old:
One 5ml spoonful three times a day.

The above doses may be taken before or after meals.

Children aged 6 months - 2 years old:
Half to One 5ml spoonful three or four times a day. This should be given 15 minutes before feeding. Do not give more than four 5ml spoonfuls in any one day.

If you take more Dicycloverine Oral Solution than you should:
It is important to stick to the dose on the label of the medicine. If you or someone else takes too much medicine, contact your doctor or nearest hospital emergency department immediately. Always take any medicine left over with you and also the box, as this will allow easier identification of the medicine.

If you forget to take Dicycloverine Oral Solution:
If you forget to take a dose, take it as soon as you remember. If it is almost time for your next dose, do not take a double dose to make up for the forgotten dose, just carry on as before.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Dicycloverine Oral Solution can cause side effects although not everybody gets them.

Some people may feel dizzy, thirsty, or have a dry mouth:

Rarity the following may occur:
- Drowsiness/fatigue
- Blurred vision
- Constipation
- Numbness or loss of appetite
- Headache
- Nausea
- Difficulty in passing urine

If you experience any of the above problems or any other unwanted effects, tell your doctor or pharmacist.

5. HOW TO STORE DICYCLOVERINE ORAL SOLUTION

- Keep out of the reach and sight of children.
- Do not use after the expiry date which is stated on the label and carton. The expiry date refers to the last day of the month.
- Store your medicine in the original container. Do not store above 25°C.
- 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 Dicycloverine Oral Solution contains?
The name of this medicine is Dicycloverine Oral Solution. The active substance in each tablet is dicycloverine hydrochloride. Each 5ml Spoonful contains:
- Dicycloverine hydrochloride 10mg
- Orange flavouring
- Flavouring agent
- Colour E110
- Water for injection

What Dicycloverine Oral Solution looks like and contents of the pack:
Dicycloverine Oral Solution is a pale yellow coloured, clear flavoured Solution. Each Bottle contains 120ml of Solution.

Marketing Authorisation Holder and Manufacturer:
The Marketing Authorisation holder and manufacturer of oral solution is NRIM Limited, Marlborough House, 248 Regents Park Road, Finchley, London, N3 2UA, United Kingdom.

This leaflet was prepared in 11/2008.