Ephedrine 1.0%w/v Nasal Drops

PL 00156/0035

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation (licence) for the medicinal product Ephedrine 1.0%w/v Nasal Drops (product licence number: PL 00156/0035). Ephedrine 1.0%w/v Nasal Drops are available from pharmacies without a prescription.

Ephedrine 1.0%w/v Nasal Drops are used to reduce nasal congestion (a blocked nose).

Ephedrine 1.0%w/v Nasal Drops raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.
EPHEDRINE 1.0%W/V NASAL DROPS

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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 Ephedrine 1.0%w/v Nasal Drops to Martindale Pharmaceuticals Ltd on 29 April 2010.

This is an abridged application made under Article 10.3 of EC Directive 2001/83 cross-referring to Ephedrine Nasal Drops BP 0.5% (PL 00156/0052). This application is submitted as a ‘hybrid’ application since the proposed product is a different strength to the reference product.

Ephedrine 1.0%w/v Nasal Drops are used for the relief of nasal congestion.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE
The method of manufacture of ephedrine hydrochloride is appropriate.

The proposed drug substance specification and its justification, analytical procedures and their validation, batch analyses and reference standards used by the drug substance manufacturer are satisfactory.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Active ephedrine hydrochloride is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Appropriate stability data have been generated supporting the retest period.

DRUG PRODUCT

Composition
Ephedrine 1.0%w/v Nasal Drops contain the excipients sodium chloride, benzalkonium chloride and purified water. Adequate justification was provided for the choice of excipients. Satisfactory certificates of analysis have been provided for all excipients. There were no novel excipients used and no overages.

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

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out and the results are satisfactory.

Finished product specification
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. 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 have been provided for any working standards used.

Container Closure System
The nasal drops are stored in a 10ml polyethylene dropper bottle with tamper evident cap.
Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years for unopened product and 2 months after first opening has been set, which is satisfactory. Storage conditions are “Do not store above 25°C” and “Keep container in outer carton”.

Product literature
All product literature (SPC, PIL and labelling) is satisfactory. The package leaflet was 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 it contains.

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

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

INDICATIONS
The proposed indication is as follows:

“For the relief of nasal congestion”

This is the same as the indication for the reference product and is satisfactory.

DOSE & DOSE SCHEDULE
The proposed posology section is as follows:

“Instil the drops into each nostril.

Adults (including the elderly) and children over 12 years
1-2 drops to be put into each nostril as required up to 4 times a day

Children under 12 and infants
Not recommended.

In all cases the drops should not be used for longer than 7 days.”

This is the same as the indication for the reference product and is satisfactory.

TOXICOLOGY
This has been reviewed satisfactorily.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS
Ephedrine possesses sympathomimetic properties with both weak $\alpha$- and $\beta$-adrenergic activity.

PHARMACODYNAMICS
These are reviewed sufficiently in the SPC.

BIOAVAILABILITY
The product is a preserved aqueous solution for nasal administration. Bioavailability is not an issue

BIOEQUIVALENCE
As this product is an aqueous solution no bioequivalence study is needed.

EFFICACY
Ephedrine is a well-established drug substance and no efficacy data are included in the application.

SAFETY
No safety data are needed, the product literature contains appropriate safety information.

**EXPERT REPORT**
An expert report has been compiled by a suitably qualified expert and is satisfactory.

**PRODUCT LITERATURE**
All product literature (SPC, PIL and labels) is in line with that of the reference product and is satisfactory.

**CONCLUSIONS**
A Marketing Authorisation may be granted.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Ephedrine 1.0%w/v Nasal Drops 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 applications of this type.

EFFICACY
The efficacy of ephedrine hydrochloride is well established. The SPC, PIL and labelling are satisfactory and consistent with those for the cross-reference product.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable, no significant preclinical or clinical safety concerns were identified, and benefit has been shown to be associated with ephedrine hydrochloride. The risk benefit is therefore considered to be positive.
EPHEDRINE 1.0%W/V NASAL DROPS

PL 00156/0035

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the marketing authorisation application on 21 May 2001
2 Following standard checks and communication with the applicant the MHRA considered the application valid on 19 June 2001
3 Following assessment of the application the MHRA requested further information relating to the quality dossier on 24 September 2001 and the clinical dossier on 28 September 2001
4 The applicant responded to the MHRA’s requests, providing further information on the dossier on 17 October 2001
5 Following assessment of the response the MHRA requested further information relating to the dossier on 20 December 2001 and 31 January 2002
6 The applicant responded to the MHRA’s requests, providing further information on the dossier on 25 February 2010
7 The application was determined on 29 April 2010
1 NAME OF THE MEDICINAL PRODUCT
Ephedrine 1.0%w/v Nasal Drops

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Contains Ephedrine Hydrochloride 10mg/ml
See 6.1 for excipients.

3 PHARMACEUTICAL FORM
Nasal Drops.
Ephedrine 1% Nasal Drops are a clear colourless solution

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
For the relief of nasal congestion

4.2 Posology and method of administration
Instil the drops into each nostril.

   Adults (including the elderly) and children over 12 years
   1-2 drops to be put into each nostril as required up to 4 times a day

   Children under 12 and infants
   Not recommended.

   In all cases the drops should not be used for longer than 7 days.

4.3 Contraindications
Ephedrine should not be given to patients who are being treated with
monoamine oxidase inhibitors, or within two weeks of stopping such
treatment. It should also be avoided in patients with cardiovascular disease,
hypertension, hyperthyroidism, hyperexcitability, phaeochromocytoma,
closed- angle glaucoma and urinary retention.
   Patients receiving halogenated anaesthetics (see section 4.5).
   Children under 12 years

4.4 Special warnings and precautions for use
Asthmatics should consult their doctor before using ephedrine nasal drops.

   Avoid excessive or prolonged use due risk of tolerance with diminished effect
   and risk of rebound congestion.
4.5 **Interaction with other medicinal products and other forms of interaction**
The effects of ephedrine are diminished by guanethidine, reserpine, and probably methyldopa, and may be diminished or enhanced by tricyclic antidepressants. Ephedrine may also diminish the effects of guanethidine and may increase the possibility of arrhythmias in digitalised patients.

Patients anaesthetised with inhalation anaesthetics but particularly cyclopropane and halothane can develop cardiac arrhythmias if given sympathomimetics.

4.6 **Pregnancy and lactation**
All drugs should be avoided if possible during pregnancy and lactation. Medical advice should be sought before use. Ephedrine has been reported to cause irritability and disturbed sleep when used during breast feeding.

4.7 **Effects on ability to drive and use machines**
None known.

4.8 **Undesirable effects**
Undesirable effects which may arise in patients with idiosyncrasy to ephedrine include anxiety, restlessness, nausea, muscular weakness and tremors, sweating and thirst and sometimes dermatitis. In patients with prostate enlargement, it may cause increased difficulty with micturition. Continued use of drops may aggravate the condition and lead to rebound congestion and drug induced rhinitis. It may also lead to tolerance.

Undesirable effects associated with the use of this product also include local irritation, headache and cardiovascular effects.

4.9 **Overdose**
The estimated minimal lethal dose of ephedrine in children up to 2 years of age is 200mg and for adults 2g, but fatalities due to ephedrine overdose are rare and not likely to occur following administration of nasal drops. Single doses of up to 400mg of ephedrine have been given without serious toxic effects. In large doses ephedrine may cause giddiness, headache, nausea, vomiting, sweating, thirst, tachycardia, precordial pain, palpitations, difficulty in micturition, muscular weakness and tremors, anxiety, restlessness and insomnia. Paranoid psychosis, delusions and hallucinations may follow overdose. Treatment of overdosage should include supportive and symptomatic treatment. In severe cases the stomach should be emptied by aspiration and lavage. Diazepam may be given to control central nervous system stimulation.

Chlorpromazine may be given for excitement or the management of hallucinations. A beta-adrenoceptor blocking agent may be required to control cardiac arrhythmias.

5 **PHARMACOLOGICAL PROPERTIES**
5.1 Pharmacodynamic properties
Ephedrine hydrochloride is applied locally to relieve congestion of mucous membranes in acute sinusitis and hay fever. It has a stimulant action on the respiratory centre. Ephedrine releases norepinephrine from storage sites in the sympathetic nerves to the effector organ. It exhibits tachyphylaxis, repeated infusions become less effective as the releasable stores of norepinephrine are depleted.

Ephedrine redistributes the blood flow and causes cardiac stimulation without markedly raising the blood pressure.

Sympathomimetic drugs exert their effect by vasoconstriction of the mucosal blood vessels, which in turn reduces the thickness of the nasal mucosa. However they can give rise to a rebound phenomenon as their effects wear off, due to secondary vasodilation with a subsequent temporary increase in nasal congestion.

5.2 Pharmacokinetic properties
Ephedrine is rapidly and completely absorbed from the gastrointestinal tract. It is resistant to metabolism by monoamine oxidase and is largely excreted unchanged in the urine together with small amounts of metabolites produced by hepatic metabolism. Ephedrine has been variously reported to have a plasma half-life ranging from 3 to 6 hours depending on urinary pH; elimination is enhanced and half-life accordingly shorter in acid urine.

5.3 Preclinical safety data
No additional data of relevance to the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium chloride
Benzalkonium chloride
Purified water

6.2 Incompatibilities
None stated

6.3 Shelf life
3 years (36 months)
Discard any drops 2 months after first opening.

6.4 Special precautions for storage
Do not store above 25°C keep container in outer carton.

6.5 Nature and contents of container
Polyethylene dropper bottle with tamper evident cap. Pack size 10ml.
6.6 Special precautions for disposal
Not applicable

7 MARKETING AUTHORISATION HOLDER
Martindale Pharmaceuticals Ltd
Bampton Road,
Romford,
RM3 8UG
England.

8 MARKETING AUTHORISATION NUMBER(S)
PL 00156/0035

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
29/04/2010

10 DATE OF REVISION OF THE TEXT
29/04/2010
PATIENT INFORMATION LEAFLET

Ephedrine 1% w/v Nasal Drops
(ephedrine hydrochloride)

Read all this leaflet carefully before you use Ephedrine Nasal Drops
• Keep this leaflet. You may need to read it again
• If you have any further questions, please ask your doctor or pharmacist
• This medicine has been prescribed for you and you should not pass it on to others. It may harm them, even their symptoms are the same as yours
• If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist

In this leaflet:
1. What Ephedrine Nasal Drops is and what it is used for?
2. Before Ephedrine Nasal Drops is used
3. How will Ephedrine Nasal Drops be used?
4. Possible Side effects
5. Storing Ephedrine Nasal Drops
6. Further information

1. WHAT EPHEDRINE NASAL DROPS ARE AND WHAT THEY ARE USED FOR?

Ephedrine belongs to a group of medicines called sympathomimetics. A sympathomimetic is a medicine which has a wide range of effects. In this case it reduces nasal congestion (blocked nose).

Ephedrine Nasal Drops are used to treat congestion in the nose otherwise known as a blocked nose.

2. BEFORE EPHEDRINE NASAL DROPS ARE USED

DO NOT use Ephedrine Nasal Drops if:
You are allergic (hypersensitive) to Ephedrine or to the ingredients present in the product (see section 6).

TAKE SPECIAL CARE with Ephedrine if:
• You are pregnant, planning to become pregnant or are breast feeding
• You suffer from diabetes, glaucoma, an over-active thyroid gland, prostate gland enlargement and any cardiovascular disease or heart condition.

If any of the above applies to you or your child, please consult your doctor.

Taking other medicines
Tell your doctor if you are taking anti-depressants including any monoamine oxidase inhibitors or recently stopped taking, within the last 2 weeks.
If you are going to have an operation or medical procedure using an anaesthetic agent you should tell your doctor or anaesthetist if you are using ephedrine nasal drops

Pregnancy and breast-feeding:
This medicine should not be given to you if you are pregnant, trying to become pregnant or are breast-feeding, unless your doctor has recommended it.

Driving and using machines:
This medicine does not affect your ability to drive or operate machinery.

3. HOW WILL EPHEDRINE NASAL DROPS BE USED?

• Always follow the instruction of your doctor or pharmacist.
• For nasal use only.
• These drops are used by tilting back the head and carefully squeezing the bottle so that the required number of drops are applied to each nostril.
• You may find it easier to get someone to help you.
Adults (including the elderly) and children over 12 years

- 1 or 2 drops to be put into each nostril as required up to 4 times a day

Children under 12 years (including infants)

- Not recommended.

You should not continue to take this medicine for more than 7 days without seeking medical advice.

If you forget to take Ephedrine Nasal Drops
Try not to miss a dose. Do not worry, just carry on as normal. Do not use extra drops to make up.

If you use more Ephedrine Nasal Drops than you should
If you suspect someone has swallowed any Ephedrine Nasal Drops, contact your doctor or go to the accident and emergency department of your hospital at once. Always take the container with you, if possible, even if empty.

4. POSSIBLE SIDE EFFECTS

Like all medicines Ephedrine Nasal Drops can sometimes cause side effects, although not everyone gets them.

They may include:
- Anxiety
- Restlessness
- Headache
- Nausea
- Weakness and trembling
- Itchiness of the nose
- Sweating and thirst
- Effects on the heart and circulation e.g. high blood pressure
- Inflammation of the skin

People with difficulty in passing urine may find that the condition gets worse.

Use of the drops for more than 7 days may make your congestion worse and the effectiveness of the drops will decrease.

If you notice these or any side effects not included above, stop use and tell your doctor or pharmacist. They will tell you what to do.

5. STORING EPHEDRINE NASAL DROPS

- This product has an expiry date printed on the bottle label. The expiry date refers to the last day of the month.
- If you have any unused drops 2 months after first opening they should be discarded. Medicines should not be disposed of in sewage or household waste. Ask your pharmacist how to dispose of the medicines no longer required. The measures will help protect the environment.
- Do not store above 25°C, protect from light.
- Keep all medicines out of the reach and sight of children.

6. FURTHER INFORMATION

What Ephedrine Nasal Drops contains

The active ingredient is Ephedrine Hydrochloride 1% w/v.

Other ingredients are Purified Water, Sodium Chloride and Benzalkonium Chloride 0.01% w/v.

Contents of the pack

Ephedrine nasal drops are a clear colourless liquid. Each bottle contains 10ml.

Marketing Authorisation Holder and Manufacturer:

Martindale Pharmaceuticals Ltd, Bampton Road, Rainford, RM3 8UG, England

Product Licence No. PL 00156/0035

Date of approval: 01/2010

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LABELLING

Label: