

**Public Assessment Report**  
**Decentralised Procedure**

**Pyridostigmine 60mg Tablets**

**Procedure No: UK/H/1210/001/DC**

**UK Licence No: PL 41830/0016**  
**(previously PL 20620/0036)**

**NRIM Limited**

## LAY SUMMARY

This is a summary of the Public Assessment Report (PAR) for Pyridostigmine 60mg Tablets. It explains how Pyridostigmine 60mg Tablets (PL 41830/0016, previously PL 20620/0036; UK/H/1210/001/DC) was assessed and the authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Pyridostigmine 60mg Tablets.

For practical information about using Pyridostigmine 60mg Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

### **What are Pyridostigmine 60mg Tablets and what are they used for?**

Pyridostigmine 60 mg tablets is a 'generic' medicine. This means that Pyridostigmine 60 mg tablets are similar to a reference medicine already authorised in the European Union (EU) called Mestinon 60mg Tablets (Meda Pharmaceuticals Limited, previously known as Valeant Pharmaceuticals Limited prior to an approved name change on 23 February 2009). Mestinon 60mg Tablets were first granted a Licence of Right to Roche Product Limited in 07 August 1996 and subsequently underwent a Change of Ownership procedure to ICN Pharmaceuticals Limited on 01 March 1998. The Marketing Authorisation Holder was later changed to Valeant Pharmaceuticals Limited on 11 June 2004.

Pyridostigmine 60mg Tablets contain the active ingredient, pyridostigmine (as pyridostigmine bromide) and are used to treat:

- Myasthenia gravis, a condition that prevents messages reaching the muscles from the brain. The muscles quickly become tired and weak and, in severe cases may become paralysed.
- Some rare forms of constipation (paralytic ileus).
- The inability to pass urine after an operation.

### **How are Pyridostigmine 60mg Tablets used?**

Pyridostigmine 60mg Tablets can only be obtained on prescription. This medicine should be taken exactly as advised by the prescribing doctor.

Pyridostigmine 60mg Tablets are taken by mouth. The tablets should be swallowed with water or another non-alcoholic drink. Pyridostigmine tablets should be taken 30 to 60 minutes before a meal. The dose is dependent on the illness and the age of the patient.

For further information on how Pyridostigmine 60mg Tablets are used, please see the Summary of Product Characteristics available on the MHRA website.

### **How do Pyridostigmine 60 mg Tablets work?**

The active ingredient, pyridostigmine, belongs to the group of medicines known as anticholinesterase inhibitors. Pyridostigmine helps messages pass more easily from the brain to the muscles so that the muscles work properly.

### **How have Pyridostigmine 60mg Tablets been studied?**

As Pyridostigmine 60mg Tablets is a generic medicine, studies in patients have been limited to tests to determine that the tablets are similar to the reference medicine, Mestinon 60mg Tablets (Meda Pharmaceuticals Limited). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

In addition, the company (NRIM Limited) provided data from the published literature on pyridostigmine.

**What are the benefits and risks of Pyridostigmine 60mg Tablets?**

Because Pyridostigmine 60mg Tablets is a generic medicine that is bioequivalent to the reference medicine, the benefits and risks are taken as being the same as that for the reference medicine.

**Why are Pyridostigmine 60mg Tablets approved?**

It was concluded that, in accordance with EU requirements, Pyridostigmine 60mg Tablets have been shown to have comparable quality and to be bioequivalent to Mestinon 60mg Tablets (Meda Pharmaceuticals Limited). Therefore, the view was that, as Mestinon 60mg Tablets (Meda Pharmaceuticals Limited), the benefits outweigh the identified risks.

**What measures are being taken to ensure the safe and effective use of Pyridostigmine 60mg Tablets?**

Safety information has been included in the Summary of Product Characteristics and the package leaflet for Pyridostigmine 60mg Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

**Other information about Pyridostigmine 60mg Tablets.**

A Marketing Authorisation (PL 20620/0036; UK/H/1210/001/DC) was first granted in the UK to NRI Limited on 29 August 2008.

Subsequent to a Change of Ownership procedure and changes in the name of the authorisation holder, the Marketing Authorisation (PL 41830/0016) was granted to NRI Limited on 06 March 2013.

The full PAR for Pyridostigmine 60mg Tablets follows this summary.

For more information about treatment with Pyridostigmine 60mg Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in June 2014.

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## Module 1

### Information about the initial procedure

Product Name	Pyridostigmine 60mg Tablets
Type of Application	Article 10.1, Generic Application
Active Substance	Pyridostigmine
Form	Tablet
Strength	60mg
MA Holder	NRIM Limited Marlborough House 298 Regents Park Road London N3 2UA UK
Reference Member State	United Kingdom
Concerned Member States	Ireland
Procedure Number	UK/H/1210/001/DC
Timetable	Day 210 – 31 July 2008

## **Module 2**

# **Summary of Product Characteristics**

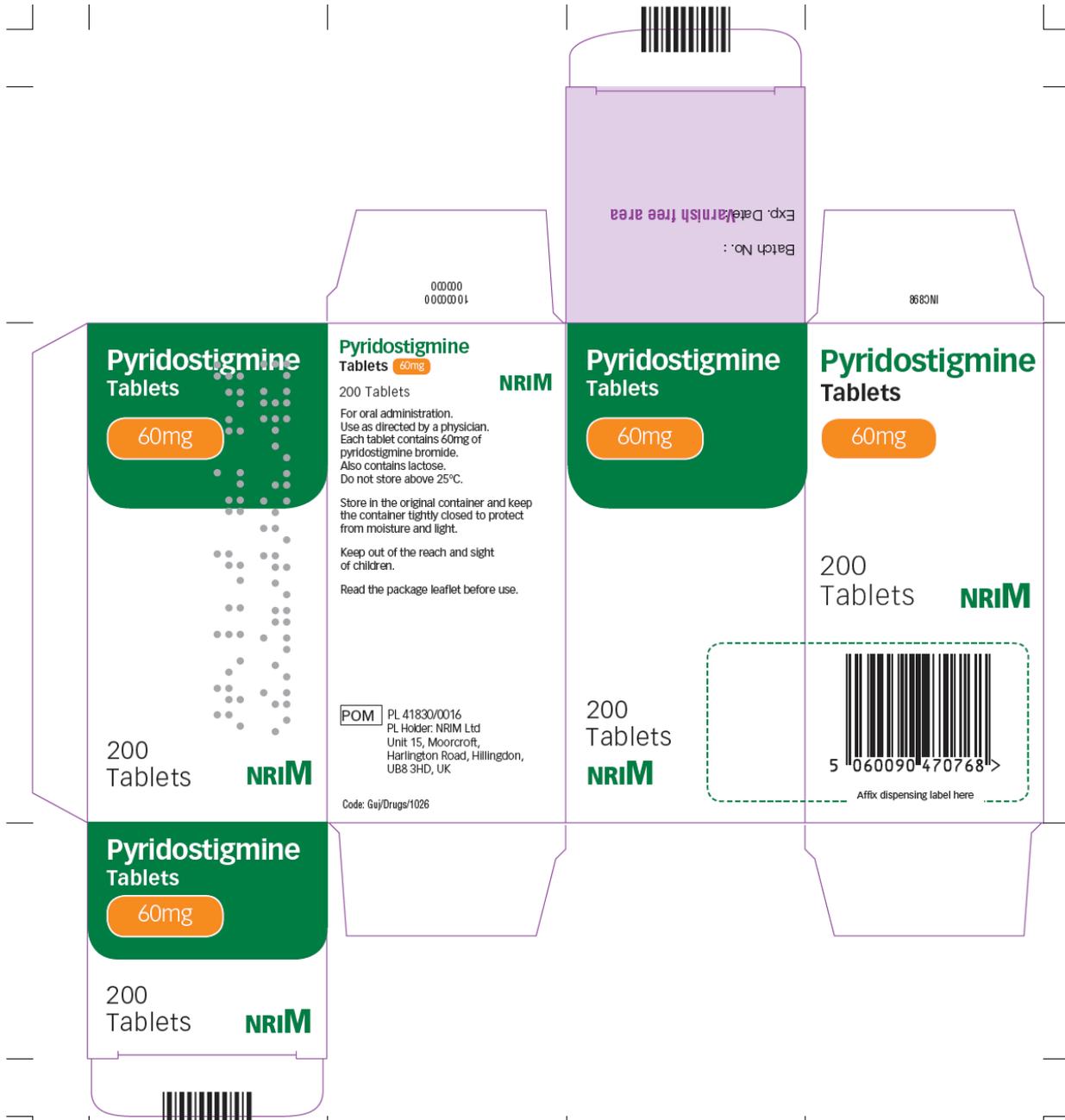
In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

## **Module 3**

# **Patient Information Leaflet**

In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

# Module 4 Labelling



<b>Pyridostigmine Tablets</b> 60mg		200 Tablets	Batch No.: Varnish free area Exp. Date:
For oral administration. Use as directed by a physician. Each tablet contains 60mg pyridostigmine bromide.  Also contains lactose.	Do not store above 25°C. Store in the original container. Keep the container tightly closed. <b>Keep out of the reach and sight of children.</b> Read the package leaflet before use.		
<b>NRIM</b>	[POM] PL 41830/0016 PL Holder: NRIM Ltd, Unit 15, Moorcroft, Harlington Road, Hillingdon, UB8 3HD, UK		

## Module 5

### Scientific discussion during the initial procedure

#### I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a Marketing Authorisation for the medicinal product Pyridostigmine 60mg Tablets (PL 20620/0036) on 29 August 2008. The product is a prescription only medicine.

This application was made under Article 10.1 of 2001/83 EC, as amended, claiming that Pyridostigmine 60mg Tablets is a generic product of Mestinon 60mg tablets (Roche Products Ltd), which was granted a Licence of Right on 07 August 1986. The licence subsequently underwent a Change of Ownership procedure to ICN Pharmaceuticals Limited on 01 March 1998. On 11 June 2004, the Marketing Authorisation Holder was further changed to Valeant Pharmaceuticals Limited, which underwent a change of name to Meda Pharmaceuticals Limited (the current Marketing Authorisation Holder) on 23 February 2009. The reference product has therefore been authorised in the EEA for at least 10 years.

The product contains the active ingredient pyridostigmine and is indicated for myasthenia gravis, paralytic ileus and post-operative urinary retention.

Pyridostigmine is an anticholinesterase. Therefore, the action of pyridostigmine can briefly be described as the potentiation of naturally occurring acetylcholine by preventing its breakdown by cholinesterase.

No new preclinical studies were conducted, which is acceptable given that the application referred to a product that has been licensed for over 10 years.

No clinical studies were conducted, which is acceptable given that the application referred to a product that has been licensed for over 10 years. The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of the product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites.

The Decentralised Procedure was completed at Day 210 (31 July 2008), with the RMS and the CMS agreeing that the licence was approvable. The national phase of the Decentralised Procedure was completed in the UK on 29 August 2008.

Subsequent to a Change of Ownership procedure and changes in the name of the authorisation holder, the Marketing Authorisation (PL 41830/0016) was granted to NRIM Limited on 06 March 2013.

**II ABOUT THE PRODUCT**

Name of the product in the Reference Member State	Pyridostigmine 60mg Tablets
Name(s) of the active substance(s) (INN)	Pyridostigmine
Pharmacotherapeutic classification (ATC code)	Anticholinesterases (N07 A A 02)
Pharmaceutical form and strength(s)	60mg Tablet
Reference number for the Decentralised Procedure	UK/H/1210/001/DC
Reference Member State	United Kingdom
Concerned Member State	Ireland
Marketing Authorisation Number(s)	PL 20620/0036
Name and address of the authorisation holder	NRIM Limited Marlborough House 298 Regents Park Road London N3 2UA UK

### **III SCIENTIFIC OVERVIEW AND DISCUSSION**

#### **III.1 QUALITY ASPECTS**

##### **DRUG SUBSTANCE**

##### **Pyridostigmine Bromide**

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 specifications are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification based on the European Pharmacopeia specification is provided for pyridostigmine bromide.

Analytical methods have been validated and are satisfactory for ensuring compliance with the relevant specifications.

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

Pyridostigmine bromide is stored in appropriate packaging.

Stability data have been generated which support a retest period of 60 months when stored in an airtight container, protected from light.

##### **DRUG PRODUCT**

##### **Other Ingredients**

The excipients present are silicon dioxide, lactose monohydrate, maize starch, purified talc and magnesium stearate.

The excipients used comply with their respective international monographs. Satisfactory certificates of analysis have been provided.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption.

##### **Pharmaceutical Development**

The applicant has provided suitable product development rationale and data.

##### **Impurity Profile**

Comparative impurity profiles for the reference product and test product are provided. The test product has a better profile than the reference product.

##### **Dissolution Profile**

Comparative dissolution profiles were generated for the reference product and the test product showing that they have similar release profiles. The dissolution method used was appropriate.

##### **Manufacture**

Satisfactory batch formulae have been provided for the manufacture of the product along with an appropriate account of the manufacturing process. Suitable in-process controls are applied during the manufacturing process to ensure the quality of the product.

The manufacturing process has been validated and the results are satisfactory.

**Control of Drug Product**

The proposed finished product specifications are acceptable and provide an assurance of the quality of the finished products. The analytical methods used have been suitably validated. Batch analysis data have demonstrated compliance with the proposed specifications.

**Reference Standards or Materials**

Certificates of analysis for all reference standards used have been provided and are satisfactory.

**Container Closure System**

The finished product is packaged in a type III amber glass bottle or a white opaque HDPE bottle containing a HDPE desiccant (silica gel) canister, each with a polypropylene child-resistant closure. Each bottle contains 200 tablets. Satisfactory specifications and certificates of analysis have been provided for the packaging components.

**Stability of the Drug Product**

The stability data provided support a shelf-life of 15 months, with storage conditions 'Do not store above 25°C. Store in the original container and keep container tightly closed to protect from moisture and light'.

**Bioequivalence/Bioavailability**

Refer to the clinical assessment.

**SPC, PIL, Labels**

The SPC and labels are pharmaceutically acceptable.

The Patient Information Leaflet (PIL) is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL 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 on the information that it contains.

**CONCLUSION**

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

**III.2 NON-CLINICAL ASPECTS**

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

The non-clinical overview provides a satisfactory review of the relevant preclinical pharmacological and toxicological literature.

The grant of a Marketing Authorisation is recommended for this application.

### III.3 CLINICAL ASPECTS

#### CLINICAL PHARMACOLOGY

The applicant has submitted two bioavailability studies, one fasted and one fed.

#### Study 1

A randomised single dose, two treatment, two period, two sequence, single dose, crossover study, with a seven day washout under fasting conditions which compared the bioavailability of Pyridostigmine 60mg Tablets (NRIM Ltd) and Mestinon 60mg tablets (Valeant Pharmaceuticals Ltd). Twenty-four healthy adult males were enrolled in the study. A single oral dose was administered after an overnight fast of 10 hours. Samples were collected at intervals up to 24 hours post dosing in each period. The pharmacokinetic parameters  $C_{max}$ ,  $T_{max}$ ,  $AUC_{0-t}$ ,  $AUC_{0-inf}$ ,  $K_{el}$  and  $T_{1/2}$  were determined.

Results:

	Pyridostigmine 60mg (Test)	Mestinon 60mg (Reference)	Test/Ref (90% CI)
$AUC_{0-t}$ (ng.hr/ml)	190.22 +/- 17.08	198.13 +/- 25.80	88.98% to 116.57%
$AUC_{0-inf}$ (ng.hr/ml)	160.90 +/- 15.97	160.90 +/- 15.97	89.91% to 124.46%
$C_{max}$ (ng/ml)	43.41 +/- 4.26	45.09 +/- 7.40	89.60% to 125.85%

$C_{max}$  maximum plasma concentration

$AUC_{0-t}$  area under the plasma concentration-time curve from time zero to t hours

$AUC_{0-inf}$  area under the plasma concentration-time curve from time zero to infinity hours

**Conclusions from the biostudy:** The AUCs are within the 90% confidence intervals, but the  $C_{max}$  90% upper limit is exceeded, albeit only slightly. The fasting environment is potentially a more sensitive test for bioequivalence than the fed study. The applicant has provided a suitable argument to justify why the upper limit for  $C_{max}$  may not be of clinical relevance and should have no safety or efficacy consequences.

#### Study 2

A randomised single dose, two treatment, two period, two sequence, single dose, crossover study, with a seven day washout under fed conditions which compared the bioavailability of Pyridostigmine 60mg Tablets (NRIM Ltd) and Mestinon 60mg tablets (Valeant Pharmaceuticals Ltd). Twenty-four healthy adult males were enrolled in the study. A single oral dose was administered after an overnight fast of 10 hours following a standardised meal. Samples were collected at intervals up to 24 hours post dosing in each period. The pharmacokinetic parameters  $C_{max}$ ,  $T_{max}$ ,  $AUC_{0-t}$ ,  $AUC_{0-inf}$ ,  $K_{el}$  and  $T_{1/2}$  were determined.

Results:

	Pyridostigmine 60mg (Test)	Mestinon 60mg (Reference)	Test/Ref (90% CI)
$AUC_{0-t}$ (ng.hr/ml)	193.44 +/- 18.94	187.71 +/- 14.95	92.90% to 114.66%
$AUC_{0-inf}$ (ng.hr/ml)	142.52 +/- 13.48	134.91 +/- 10.87	89.93% to 109.25%
$C_{max}$ (ng/ml)	24.1 +/- 1.38	45.09 +/- 7.40	97.17% to 110.04%

$C_{max}$  maximum plasma concentration

$AUC_{0-t}$  area under the plasma concentration-time curve from time zero to t hours

$AUC_{0-inf}$  area under the plasma concentration-time curve from time zero to infinity hours

**Conclusions from the biostudy:** The AUCs and  $C_{max}$  are within the 90% confidence intervals.

**Overall conclusion on the biostudies:** Bioequivalence has been demonstrated.

**EFFICACY**

No new efficacy data have been provided and none are required for an application of this type. However, the applicant has provided a review of clinical trials published in the literature confirming the efficacy and safety of pyridostigmine bromide.

**SAFETY**

No new safety data have been provided and none are required for an application of this type. However, the applicant has provided a literature safety review of pyridostigmine bromide. No new safety issues have been identified.

**EXPERT REPORT**

A satisfactory clinical expert report has been submitted, which has been written by an appropriately qualified medical doctor.

**SUMMARY OF PRODUCT CHARACTERISTICS (SPC)**

This is satisfactory and consistent with the SPC for the reference product.

**PATIENT INFORMATION LEAFLET (PIL)**

This is satisfactory and consistent with the SPC.

**LABELLING**

This is satisfactory.

**PHARMACOVIGILANCE**

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.

**CONCLUSION**

The application contains an adequate review of published clinical data and bioequivalence to the reference product has been shown. Approval is recommended from the clinical point of view.

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

##### **QUALITY**

The important quality characteristics of Pyridostigmine 60mg Tablets 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**

Bioequivalence has been demonstrated between the applicant's Pyridostigmine 60mg Tablets and Mestinon 60mg tablets (Valeant Pharmaceuticals Ltd).

No new or unexpected safety concerns arose from this application.

The SPC, PIL and labelling are satisfactory and consistent with those for the reference product.

##### **RISK BENEFIT ASSESSMENT**

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's product and the reference product are interchangeable. Clinical experience with pyridostigmine bromide is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

## Module 6

### Steps Taken After Initial Procedure - Summary

<b>Date submitted</b>	<b>Application type</b>	<b>Scope</b>	<b>Outcome</b>
10 February 2014	Type II	To submit a Bioequivalence (BE) Fasting Study to determine whether the medicinal product is essentially similar to 'Mestinon 60mg Tablets' (Meda Pharmaceuticals Limited, previously known as, Valeant Pharmaceuticals Ltd., UK).	Approved on 21 April 2014

## Annex 1

<b>Our Reference:</b>	<b>PL 41830/0016, Application 0014</b>
<b>Product:</b>	<b>Pyridostigmine 60mg Tablets</b>
<b>Marketing Authorisation Holder:</b>	<b>NRIM Limited</b>
<b>Active Ingredient(s):</b>	<b>Pyridostigmine bromide</b>
<b>Type of Procedure:</b>	<b>Mutual Recognition</b>
<b>Submission Type:</b>	<b>Variation</b>
<b>Submission Category:</b>	<b>Type II</b>
<b>Submission Complexity:</b>	<b>Complex</b>
<b>EU Procedure Number (if applicable):</b>	<b>UK/H/1210/001/II/019</b>

### Reason:

To submit a Bioequivalence (BE) Fasting Study to determine whether the medicinal product is essentially similar to 'Mestinon 60mg Tablets' (Meda Pharmaceuticals Limited, previously known as Valeant Pharmaceuticals Ltd., UK).

### Supporting Evidence

The results of a randomised, single-dose, two period, two treatment, two sequence, cross-over study comparing the test product Pyridostigmine 60mg tablets and the reference product Mestinon 60mg tablets (Meda Pharmaceuticals Ltd., UK) under fasting conditions.

### Evaluation

The subjects were administered a single dose of either the test or the reference product with 240 ml of water, after a 12-hour overnight fast. Blood sampling was performed pre-dose and up to 24 hours post-dose in each treatment period. The washout period between the two treatment arms was 7 days. The pharmacokinetic results are presented below:

Parameters (Units)	Ratio of Geometric Least Squares Means			90% Confidence Limits (%)
	Test product (T)	Reference product (R)	(T / R) %	(T vs. R)
C <sub>max</sub> (ng / mL)	37.528	39.259	95.6	84.22-108.50
AUC <sub>0-t</sub> (ng . hr/ mL)	185.310	182.944	101.3	92.82-110.54
AUC <sub>0-inf</sub> (ng . hr/mL)	191.846	188.690	101.7	93.44-110.63

C<sub>max</sub> maximum plasma concentration

AUC<sub>0-t</sub> area under the plasma concentration-time curve from time zero to t hours

AUC<sub>0-inf</sub> area under the plasma concentration-time curve from time zero to infinity hours

The *Guidance on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev 1, Corr\*\*) defines the 90% confidence limits as 80.00% to 125.00% for C<sub>max</sub> and AUC values. The 90% confidence intervals of the test/reference ratio for C<sub>max</sub> and AUC values lie within the acceptable limits for pyridostigmine. Thus, the data support the claim that the applicant's test product is bioequivalent to the reference product Mestinon 60mg tablets (Meda Pharmaceuticals Ltd., UK), under fasting conditions.

### Safety

No new or unexpected safety issues arose during the bioequivalence study.

### Conclusion

Bioequivalence has been demonstrated between the applicant's Pyridostigmine 60 mg tablets and the reference Mestinon 60mg tablets by Meda Pharmaceuticals Ltd, under fasting conditions.

**Decision** – Approved on 21 April 2014.