Glycopyrronium Bromide 1mg Tablets
Glycopyrronium Bromide 2mg Tablets

(Glycopyrronium bromide)

PL 20117/0094-0095

UKPAR

Morningside Healthcare Limited.
LAY SUMMARY

Glycopyrronium Bromide 1mg and 2mg Tablets
(Glycopyrronium bromide, tablets, 1mg and 2mg)

This is a summary of the Public Assessment Report (PAR) for Glycopyrronium Bromide 1mg and 2mg Tablets (PL 20117/0094-0095). It explains how Glycopyrronium Bromide 1mg and 2mg Tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Glycopyrronium Bromide 1mg and 2mg Tablets.

For practical information about using Glycopyrronium Bromide 1mg and 2mg Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

The products may be referred to as Glycopyrronium Bromide Tablets in this report.

What are Glycopyrronium Bromide Tablets and what are they used for?
Glycopyrronium Bromide Tablets contain the active substance glycopyrronium bromide. The tablets are used together with other medicines to help treat peptic (stomach) ulcers in adults.

Glycopyrronium bromide–containing products have been available in the European Union for the proposed indications in adults for many years.

How are Glycopyrronium Bromide Tablets tablets used?
Glycopyrronium Bromide Tablets are taken by mouth. The recommended dose for adults is:

Glycopyrronium Bromide 1mg Tablets
One tablet, three times daily (in the morning, early afternoon and at bedtime). Some patients may require two tablets at bedtime to control symptoms overnight. When symptoms are controlled, a dose of one tablet twice a day may be sufficient.

Glycopyrronium Bromide 2mg Tablets
One tablet, two or three times a day at equally spaced intervals. The score line is not intended for breaking the tablet.

Glycopyrronium Bromide Tablets are not recommended for use in children.

For further information on how Glycopyrronium Bromide Tablets are used, please refer to the Summaries of Product Characteristics and the Patient Information Leaflet available on the MHRA website.

Glycopyrronium Bromide Tablets can only be obtained on prescription.

How do Glycopyrronium Bromide Tablets work?
The active substance, glycopyrronium bromide, belongs to a group of medicines called anticholinergic or antimuscarinic drugs. It makes the stomach contents less acid.
How have Glycopyrronium Bromide Tablets been studied?
As glycopyrronium bromide is a well-known substance, and its use in the treatment of peptic ulcers in adults is well established, the applicant (Morningside Healthcare Limited) presented data from the scientific literature. The literature provided confirmed the efficacy and safety of glycopyrronium bromide in the treatment of peptic (stomach) ulcers in adults.

What are the risks of Glycopyrronium Bromide Tablets?
Like all medicines, this medicine can cause side effects, although not everybody gets them.

For information about side effects that may occur with using Glycopyrronium Bromide Tablets, please refer to the package leaflet or the Summaries of Product Characteristics available on the MHRA website.

Why are Glycopyrronium Bromide Tablets approved?
The use of Glycopyrronium Bromide Tablets in the treatment of peptic (stomach) ulcers in adults is well-established in medical practice and documented in the scientific literature. No new or unexpected safety concerns arose from these applications. It was, therefore, considered that the benefits of Glycopyrronium Bromide Tablets outweigh the risks and the grant of Marketing Authorisations was recommended.

What measures are being taken to ensure the safe and effective use of Glycopyrronium Bromide Tablets?
A Risk Management Plan has been developed to ensure that Glycopyrronium Bromide Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Glycopyrronium Bromide Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Glycopyrronium Bromide Tablets.
Marketing Authorisations were granted in the UK on 06 February 2014.

The full PAR for Glycopyrronium Bromide Tablets follows this summary.

For more information about treatment with Glycopyrronium Bromide Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in March 2014.
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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products
Regulatory Agency (MHRA) granted Morningside Healthcare Limited Marketing Authorisations for the
medicinal products Glycopyrronium Bromide 1mg and 2mg Tablets (PL 20117/0094-0095) on
06 February 2014. The products are prescription-only medicines (POM) indicated for use adults as
add-on therapy in the treatment of peptic ulcer.

The applications were submitted under 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. Glycopyrronium-containing products have been available in the European Union for many years and
have an established favourable risk-benefit profile.

The active ingredient, glycopyrronium bromide, is a quaternary ammonium antimuscarinic agent. Its
effects are similar to those of atropine. Antimuscarinic drugs are competitive inhibitors of the actions of
acetylcholine at the muscarinic receptors of autonomic effector sites innervated by parasympathetic
(cholinergic postganglionic) nerves.

Bibliographic literature data on glycopyrronium bromide have been submitted to support these
applications. No new non-clinical or clinical studies were conducted for these applications, which is
acceptable given that these are bibliographic applications for products containing an active ingredient of
well-established use.

No new or unexpected safety concerns arose during review of information provided by the Marketing
Authorisation Holder and it was, therefore, judged that the benefits of taking Glycopyrronium Bromide
1mg and 2mg Tablets outweigh the risks and Marketing Authorisations were granted.
II QUALITY ASPECTS

II.1 Introduction
Each tablet contains 1mg or 2mg glycopyrronium bromide as the active ingredient. Other ingredients consist of the pharmaceutical excipients lactose monohydrate, dibasic calcium phosphate, povidone, sodium starch glycolate and magnesium stearate. Appropriate justification for the inclusion of each excipient has been provided.

The tablets are packed in aluminium blisters, in pack sizes of 10, 14, 28, 30, 56, 60, 90 and 112 tablets. Not all pack sizes may be marketed. 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.

II.2. Drug Substance
INN: Glycopyrronium bromide
Chemical name: (3RS)-3-[(2SR)-(2-Cyclopentyl-2-hydroxy-2-phenylacetyl)oxy]-1,1-dimethylpyrrolidinium bromide.

Structure:

Molecular formula: C_{19}H_{28}BrNO_{3}
Molecular weight: 398.3
Appearance: White or almost white crystalline powder
Solubility: Freely soluble in water, soluble in ethanol (96%) and very slightly soluble in methylene chloride.

Glycopyrronium bromide is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been described adequately 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. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been validated appropriately and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working reference standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated to support the retest period when stored in the proposed packaging.
II.3. Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate safe efficacious, stable tablets containing 1 mg and 2 mg of glycopyrronium bromide.

Suitable pharmaceutical development data have been provided for these applications.

All excipients comply with their respective European Pharmacopoeia monographs.

Satisfactory Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specifications.

With the exception of lactose monohydrate, none of the excipients contain material of animal or human origin. The supplier of lactose monohydrate has confirmed that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as intended for human consumption. In addition, the supplier has confirmed that no ruminant material, other than calf rennet, is used during the production of lactose monohydrate.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Manufacture of the product
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing processes. The manufacturing processes have been validated with full-scale production-scale batches that have shown satisfactory results.

Finished Product Specification
The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Stability of the Product
Finished 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 3 years, with no special storage conditions.

Suitable post approval stability commitments have been provided to continue stability studies on batches of finished product.

Bioequivalence
A bioequivalence study was not necessary to support applications of this type.

Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labelling are satisfactory from a pharmaceutical perspective.

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 (Marketing Authorisation Application) Forms
The MAA forms are satisfactory from a pharmaceutical perspective.
Expert Report (Quality Overall Summary)
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of Marketing Authorisations is recommended.
III  NON-CLINICAL ASPECTS

III.1  INTRODUCTION

As the pharmacodynamic, pharmacokinetic and toxicological properties of glycopyrronium bromide are well-known, no further non-clinical studies are required and none have been provided.

NON-CLINICAL EXPERT REPORT (NON-CLINICAL OVERVIEW)
The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2  Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3  Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4  Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5  Ecotoxicity/environmental risk assessment (ERA)
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As these are applications for products containing an active ingredient of well-established use; no increase in environmental burden is anticipated.

III.6  Discussion on the non-clinical aspects
The grant of Marketing Authorisations is recommended.
IV  CLINICAL ASPECTS

IV.1  Introduction
No new clinical pharmacology data have been submitted and none are required for applications of this type. The clinical pharmacology of glycopyrronium bromide is well-known.

IV.2  Pharmacokinetics
No new pharmacokinetic data were submitted and none were required for an application of this type.

IV.3  Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for an application of this type.

IV.4  Clinical efficacy
No new efficacy data have been submitted and none are required for applications of this type. The clinical efficacy of glycopyrronium bromide is well-established. Efficacy is adequately reviewed in the clinical overview.

IV.5  Clinical safety
No new safety data were supplied or required for these bibliographic applications. Safety is adequately reviewed in the clinical overview. The safety profile of glycopyrronium bromide is well-known.

IV.6  Risk Management Plan (RMP) and Pharmacovigilance system
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.

A satisfactory Risk Management Plan has been provided.

SUMMARIES OF PRODUCT CHARACTERISTICS (SmPCs), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING
The SmPCs, PIL and labels are acceptable from a clinical perspective. The PIL is consistent with the details in the SmPCs and in line with the current guidance. The labelling is in line with the current guidance.

CLINICAL EXPERT REPORT (CLINICAL OVERVIEW)
The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

IV.7  Discussion on the clinical aspects
The grant of Marketing Authorisations is recommended.

V  User consultation
The package leaflet has been evaluated via a user consultation study, in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability, as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.
VI  Overall conclusion, benefit/risk assessment and recommendation

QUALITY
The important quality characteristics of Glycopyrronium Bromide 1mg and 2mg 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.

NON-CLINICAL
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of glycopyrronium bromide are well-known, no additional data were required.

EFFICACY
No new clinical data were submitted and none were required for applications of this type.

The published literature supports the efficacy of these products in the proposed indications. The efficacy of glycopyrronium bromide is well-known. The presented evidence for well-established use of the active substance is sufficient.

SAFETY
The safety profile of glycopyrronium bromide is well-known. The literature review identified no new or unexpected safety issues or concerns.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory and in line with current guidance.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with glycopyrronium bromide is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is, therefore, considered to be positive.
Summaries of Product Characteristics (SmPC), Patient Information Leaflets (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for this medicine is presented below:
Each tablet contains 2 mg Glycopyrronium Bromide. This medicine also contains lactose. Read the package leaflet for further information. For oral use. Take as directed by your doctor. Read the package leaflet before use.

KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

This medicinal product does not require any special storage conditions.
STEPS TAKEN AFTER AUTHORISATION - SUMMARY

The following table lists non-safety variations of clinical significance to the Marketing Authorisations for these products that have been approved by the MHRA since the products were first licensed. The table includes updates that have been added as an annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to these Marketing Authorisations.

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<td>23/07/2015</td>
<td>Type II</td>
<td>PL 20117/0094-0004 &amp; PL 20117/0095-0004: To update sections 4.2 (posology and method of administration) and 6.6 (Special precautions for disposal) of the SmPC to add an additional method of administration.</td>
<td>Approved on 21/03/2016-see Annex 1</td>
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ANNEX 1

Our Reference: PL 20117/0094-0004
PL 20117/0095-0044

Product: Glycopyrronium Bromide 1mg Tablets
Glycopyrronium Bromide 2mg Tablets

Marketing Authorisation Holder: Morningside Healthcare Limited

Active Ingredient(s): Glycopyrronium Bromide

Type of Procedure: National

Submission Type: Variation

Submission Category: Type II

Submission Complexity: Standard

EU Procedure Number (if applicable): Not applicable

Reason:
To update sections 4.2 and 6.6 of the SmPC to add an additional method of administration.

Supporting Evidence
Quality overall summary, clinical overview, curriculum vitae (CV) of the quality expert, revised SmPC fragments.

Glycopyrronium Bromide 1 mg tablet (PL 20117/0094) and Glycopyrronium Bromide 2 mg tablet (PL 20117/0095) were introduced to the UK market in July 2014. Following the introduction, it became evident that there was a large usage, or requirement for usage, within the National Health Service (NHS), for dispersion/solubilisation of the tablets in water, and subsequent administration either as an oral dispersion where oral tablet administration was impracticable (i.e. dysphagia), or via a naso – gastric tube or a percutaneous endoscopic gastrostomy (PEG) tube, on the basis of documented medical enquiries received by the Marketing Authorisation Holder (MAH). Such usage cannot be recommended by the MAH, since these routes of administration are currently unlicensed.

The MAH has therefore decided to seek authorisation for such administration, as an exceptional case where oral administration of the tablet is undesirable/impracticable, by means of a variation to the marketing authorisations.

Evaluation

Clinical evaluation:

Proposed change to section 4.2 posology and method of administration
The MAH proposes adding the text:
“In exceptional instances it may not be possible to administer the tablets orally, please refer to recommendations in section 6.6 of the SmPC for administration as an extemporaneous dispersion orally. This method is also suitable for administration via nasogastric tube or percutaneous endoscopic gastrostomy (PEG) tube.”

Proposed change to section 6.6 Special precautions for disposal and other handling of the product
The MAH proposes adding the text:
“For patients where oral administration of tablet is not possible, or not desired, administration by tablet solubilisation, and subsequent administration as an extemporaneous oral dispersion, or by administration via a nasogastric tube or a percutaneous endoscopic gastrostomy (PEG) tube. Such dispersions should be administered as suggested following. For dosage recommendations see section 4.2 previously.
Dispersions of a tablet, either 1 mg or 2 mg, is done as follows, use water as a dispersant medium and a 60 ml oral syringe as the vessel for dispersion.

- Remove the plunger from the syringe and introduce a single tablet into the syringe barrel, replace the plunger and depress to just above tablet
- Draw up the required volume of water, either potable or purified is suitable, a volume of 10 ml to 30 ml is recommended, dependent upon any patient fluid intake restrictions, and manually shake the syringe assembly for 30 seconds
- Allow to stand for 5 minutes and manually shake for another 30 seconds
- Allow to stand for a further 5 minutes and manually shake for another 30 seconds
- Allow to stand for a further 5 minutes and manually shake for another 30 seconds

The tablet dispersion should be administered immediately after preparation. The dispersion is opaque, with some visible heavy particulates that are an inactive ingredient. The whole of the dispersion, including residue, is to be administered.

The studies conducted with the nasogastric and PEG tubes evaluated three types of tubing, polyvinylchloride, polyurethane and silicone, which concluded that there were no significant differences evident between the three types of tubing and showed satisfactory corresponding overall recovery levels. Similarly, filtration studies prior to analysis performed to evaluate if undissolved residues contained significant amounts of glycopyrronium bromide, concluded that there was no significant decrease in amount recovered. Filtered and unfiltered samples both showed acceptable equivalent overall recoveries.

Administration may be by the following routes:

- Administration orally, as an aqueous dispersion. Following administration of the dispersion, the oral syringe is rinsed with a further quantity of water, a minimum of 10 ml, that should also be taken to ensure complete dosing
- Administration via either a nasogastric tube, or by a PEG tube. Tubes made of polyvinylchloride, polyurethane, or silicon are suitable. There is no data available on tubes made of latex; such tubes should not be used. Immediately following administration of the initial dispersion, by connection of the oral syringe to the tube, the oral syringe is disconnected and rinsed with a further 10 ml of water, which should also be administered, in order to ensure complete dosing.

Such dispersions should not be used to provide doses below that of the tablet used to prepare the dispersion, since there is no data available to support such dose subdivision. Dispersion should be administered immediately following preparation. There is no data available to show that the medicine could be co-administered with food when administered through enteral tubes.”

Satisfactory documented evidence, from various types of health care providers, enquiring about the possibility of alternative administration though PEG or nasogastric tube was submitted. Such usage cannot be recommended by the MAH, since these routes of administration are currently unlicensed. The updated clinical overview providing the justification has been submitted. The revised quality overall summary (QOS) has also been submitted.

The MAH has summarised within the updated clinical section of the dossier a body of evidence which addresses aspects of off label administration of medication including dispersions/solutions of tablets for administration via an oral syringe, or via nasogastric or PEG tube. This includes guidance from UK sources, including widespread official NHS guidance and recommendations. On the basis of this guidance and its distribution throughout the NHS it is clear there is a large clinical and patient requirement for dispersion of oral tablets for enteral tube administration. Specifically to glycopyrronium bromide, the MAH offers evidence of enquiries made by clinical and nursing staff to its offices on the subjects of tablet crushing and dispersal. Such enquiries totalled approximately 42 % of all medical enquiries received.
The MAH also documents that requests for this information come from community pharmacies, residential care homes, GP practices, the National Pharmacy Association and the PrescQIPP NHS programme, as well as listing 24 NHS Trusts or Clinical Commissioning Groups. This evidence is sufficient to justify the clinical need for dispersal of glycopyrronium bromide and administration by way of enteric tubes.

**Quality evaluation**

Much of the pharmaceutical data in support of these variations has already been submitted and deemed satisfactory and is already included in the authorised registration dossiers.

The tablets, irrespective of strength, demonstrate rapid disintegration, and rapid dissolution. They are thus, from a physico – chemical aspect, suitable for consideration to be used to produce an extemporaneous aqueous dispersion, suitable for oral administration, administration by a nasogastric tube, or administration by a PEG tube, which are all off-licence routes of administration currently in use within the NHS, and subject to official NHS guidance. Therefore the question of extent of solubilisation, volume of water for solubilisation, and attendant stability was addressed in the submitted additional work. The analytical procedure used for determination of assay was the validated HPLC dissolution method, as authorised.

Due to the concentration resulting for analysis, i.e. a maximum of 80 microgram / ml, and a minimum of 4 microgram / ml glycopyrronium bromide, it was not possible to analyse the resultant solutions for related substances, due to limit of quantitation restrictions.

This is considered acceptable while demonstrating both content and solution stability, since the analytical procedure has been determined to be stability-indicating, during both validation and stress degradation studies, as already included and assessed in the dossier.

The experiment was conducted on sufficient replicates, for each strength, 1 mg tablet and 2 mg tablet, and evaluated significant variables, including volume for dispersion, holding times. All experimentation and sample holding and analysis were done at room temperature, i.e. 20°C to 26°C. All instrumentation and analytical equipment was suitably calibrated and qualified, as appropriate. Routine production batches were used for testing. All tablets met the predefined requirements, irrespective of time interval, or of volume of water used for dissolution. There is no evidence for any systematic degradation of the glycopyrronium content with time, nor is there any evidence of concentration dependent stability issues, and therefore tablets dissolved in potable water retain their potency in solution for at least 48 h.

The recommended 15 minute time for dispersion would seem appropriate and to have an adequate safety margin on the basis of the presented data.

Despite the stability of the resultant solution being satisfactory for up to 48 h, it is proposed that the instructions will stipulate “solutions should be freshly prepared, i.e. administration should occur immediately following the prescribed dissolution period of 15 minutes”. This is to provide an adequate safeguard against microbial contamination and proliferation, and is also in agreement with existing NHS guidance for this currently unlicensed route of administration, and will therefore be familiar to NHS personnel.

The preparation applies to both nasogastric (NG) tubes and PEG Tubes which are available in various materials of construction, commonly, polyvinylchloride, polyurethane, silicone, and latex. The MAH submitted a study to evaluate if there was any significant interaction between a dispersion of glycopyrronium bromide tablets and the materials of construction used in nasogastric and PEG tubes. In practice, latex tubes tend not to be used, due to clinical concerns over potential latex sensitivity, and
proved to be unavailable commercially, and were therefore excluded. The following tubes were evaluated:

- Polyvinylchloride
- Polyurethane
- Silicone

There are no significant differences evident between the three types of tubing that were evaluated in the study, all are giving equivalent results. Similarly, filtration prior to analysis, which was being done primarily to evaluate if undissolved residues contained significant amounts of glycopyrronium bromide, does not result in a significant decrease in amount recovered.

It is evident that compared to the results obtained immediately following dispersion in a syringe, there is a drop in the amount of glycopyrronium bromide recovered immediately following dispersion, subsequent to passage through the tubes, in general this is a consistent clinically acceptable level of the administered dose. This is most likely attributable to some degree of adsorption of the active moiety onto the plastic tubes, and evidently to a marginally greater extent than to the syringe material itself.

There is no evidence for any subsequent decrease of glycopyrronium bromide as a result of prolonged contact time with the tubes in the period of evaluation, 60 minutes, which may indicate a saturation effect of adsorption. However, in any use of these systems for administration it would be a rapid and dynamic administration, immediately followed by a flush through with water.

Some of adsorbed glycopyrronium bromide can be recovered by the subsequent use of a water flush, resulting in a slightly enhanced overall recovery for glycopyrronium bromide in a clinically acceptable range.

The tubes used differed in their lengths, polyvinylchloride tube was 100 cm, polyurethane tube was 120 cm, and silicone tube was 125 cm in length, which would result in differing surface areas of exposure for the dispersed tablets, however there does not appear to be a clear relationship or significant influence attributable to this factor.

It is concluded that using the recommended dispersion method for glycopyrronium bromide tablets, with immediate administration via a nasogastric or PEG tube constructed from polyvinylchloride, polyurethane, or silicone, and with an immediate post administration water flush of the tube, will result in a clinically acceptable percentage of the labelled claim of the dose being delivered to the patient.

A satisfactory justification in respect of clinical effectiveness, addressing physicochemical, regulatory, and biopharmaceutical aspects was submitted.

On the above basis it is considered that a therapeutically effective dose would be administered using a dispersed tablet, given via either a nasogastric or PEG tube made of polyvinylchloride, polyurethane, or silicone, followed by a post administration flush with water.

**Conclusion (clinical and quality)**

In summary, the evidence presented by the MAH is considered satisfactory. Clinical justification for the proposed amendment to the posology is accepted. On the data provided, it is considered that a therapeutically effective dose would be administered using a dispersed tablet, given via either a nasogastric or PEG tube made of polyvinylchloride, polyurethane, or silicone, followed by a post administration flush with water.

The changes to the SmPC are adequate and justified. The MAH has adequately justified reasons for not updating the PIL with additional administration details on the grounds that it may cause confusion to the
vast majority of patients prescribed the product as the additional route of administration will be used only by a very small number of patients, and initial use will be in a hospital environment under direct supervision of a healthcare professional where reference to the SmPC is the most appropriate. If following discharge, the patient is expected to self-administer, then appropriate instruction will be given by the healthcare professional.

The proposed changes to the SmPCs are acceptable. The updated SmPC fragments have been incorporated into the Marketing Authorisations.

**Decision**- Approved on 21 March 2016.