CBG MEB

# PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

# Azitromycine Mylan 200 mg / 5 ml, powder for oral suspension Mylan B.V., the Netherlands

## azithromycin (as monohydrate)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

**EU-procedure number: NL/H/958/001/MR**
**Registration number in the Netherlands: RVG 34300**

**30 June 2010**

| | |
|---|---|
| Pharmacotherapeutic group: | antibacterials for systemic use, macrolids |
| ATC code: | J01FA10 |
| Route of administration: | oral |
| Therapeutic indication: | upper respiratory tract infections (sinusitis, pharyngitis, tonsillitis), acute otitis media, lower respiratory tract infections (acute bronchitis and mild to moderately severe community acquired pneumonia), skin and soft tissue infections, uncomplicated *Chlamydia trachomatis* urethritis and cervicitis. |
| Prescription status: | prescription only |
| Date of first authorisation in NL: | 19 October 2006 |
| Concerned Member States: | Mutual recognition procedure with IT |
| Application type/legal basis: | Directive 2001/83/EC, Articles 10(1) and 10(3), depending on availability of innovator strengths in RMS and CMSs. |

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

# I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Azitromycine Mylan 200 mg/5 ml powder for oral suspension, from Mylan B.V. The date of authorisation was on 19 October 2006 in the Netherlands. The product is indicated for:

- upper respiratory tract infections: sinusitis, pharyngitis, tonsillitis
- acute otitis media
- lower respiratory tract infections: acute bronchitis and mild to moderately severe community acquired pneumonia
- skin and soft tissue infections
- uncomplicated Chlamydia trachomatis urethritis and cervicitis

A comprehensive description of the indications and posology is given in the SPC.

Azithromycin is an azalide, a sub-class of the macrolid antibiotics. By binding to the 50S-ribosomal sub-unit, azithromycin avoids the translocation of peptide chains from one side of the ribosome to the other. As a consequence of this, RNA-dependent protein synthesis in sensitive organisms is prevented.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Zithromax powder for oral suspension 200 mg/5 ml (NL RVG 14999) which has been registered in the Netherlands by Pfizer since 1994 (original product). In addition, reference is made to Zithromax authorisations in the individual member states (reference product).

Legal basis
In the Netherlands the marketing authorization is granted based on article 10(1) of directive 2001/83 EC, a so-called generic application. In Italy, where the 200 mg/5ml strength is not available, granting of the marketing authorization is based on article 10(3), a so-called hybrid apllication.
It should be mentioned that the active substance is in another salt form (as monohydrate) in comparison with the innovator product (comprising the active substance as dihydrate). Nevertheless, the products are interchangeable; the declaration of strength concerns the anhydrous substance.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Zithromax 200 mg/5 ml suspension, registered in the UK. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted.

# II SCIENTIFIC OVERVIEW AND DISCUSSION

## II.1 Quality aspects

**Compliance with Good Manufacturing Practice**
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

**Active substance**
The active substance is azithromycin monohydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). Azithromycin monohydrate is a fermentation product and appears as a white or slightly yellow crystalline powder. The macrolide nucleus comprises 10 chiral carbon atoms, the side units desosaminyl and cladinosyl possess each 4 chiral centres. No different polymorphs are described for azithromycin monohydrate.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitablity concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia, the official handbook in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Manufacture
Assessment of the manufacture was part of granting the CEP and has been approved by the EDQM.

Specification
Azithromycin monohydrate is considered adequately controlled by the CEP. Additional requirements for residual solvents and residual boron are stated on the CEP. Batch analytical data demonstrating compliance with this specification have been provided for four production scale batches.

Stability
The active substance is stable for 36 months when stored in a polyethylene bag inside an aluminium foil bag. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

** Ph.Eur., USP, BP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU, USA, or UK respectively.*

**Medicinal Product**

Composition
The product is formulated as a powder for oral suspension. The powder is packaged into 30 ml HDPE syrup bottles (capacity 60 ml), with a child resistant polypropylene closure and a polypropylene cap. The bottles contain the active ingredient azithromycin monohydrate, equivalent to azithromycin 200 mg/5 ml. The 100 mg/ 5 ml strength is only available in a 20 ml presentation whereas the 200 mg/5 ml is available in several presentations: 15 ml, 20 ml, 22.5 ml, 30 ml and 37.5 ml. Before administration the powder should be reconstituted with water.

The excipients are: sucrose, xanthan gum, hydroxypropylcellulose, trisodium phosphate anhydrous, silica, colloidal anhydrous, aspartame (E951), cream caramel flavour, and titanium dioxide (E171).

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.
The drug formulation development has been sufficiently described, discussing the influence of excipients on the conversion from azithromycin monohydrate to azithromycin dihydrate due to patent issues at the time of development.

The used excipients are well known and safe in the proposed concentrations. All excipients comply with the requirements in the relevant Ph.Eur. monographs, except for trisodium phosphate anhydrous and cream caramel which comply with in-house specifications.

Manufacturing process
A flow chart of the manufacturing process is submitted in which the points where in-process controls are performed are identified. The powder is prepared by a dry powder mixing and sieving process and consists of 5 steps in total.
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation for 3 production-scale batches will be forwarded post-approval.

Product specification
The finished product specifications are adequate to control the relevant parameters for the dosage form and includes tests for appearance, odor and taste (powder and suspension), identity, uniformity of mass, fill weight, (re)suspensibility, water, sedimentation speed, dissolution rate, microbial count, pH, assay and related substances. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analysis has been performed on production batches of all proposed packaging sizes produced at both the developing site and the production site. The batch analysis results show that the finished products meet the specifications proposed.

Packaging
The packaging material for both strengths is the same 30 ml HDPE syrup bottles (capacity 60 ml) (one size bottle for both strengths and all amounts of powder). The bottles are closed using child-resistant screw closures press and turn with guarantee ring. The applicant has committed that as soon as the tests on compliance to the revised standard ISO 8317:2003 have been completed, a declaration of compliance to this standard will be send to the MEB.

For administration after reconstitution with water an oral PE/PP-measuring syringe is enclosed in the packaging. Reconstitution could be done with this dosing syringe, even when this product will be reconstituted in the Pharmacy. In that case the patient will receive a used syringe but this is accepted because only water is used as reconstitution solvent.

Furthermore, the final volume is indicated on the label of the bottle as a control on correctness of the amount added water. A declaration with regard to the CE mark for the oral syringes is included in the dossier. A syringe adaptor is included in the syringe packaging and should be inserted into the bottle neck before dispensing. The adaptor is made of LDPE.

Stability tests on the finished product
All the presentations have been included in the stability program. To determine its stability the powder has been stored at 25°C/60% RH, 30°C/65% RH and 40°C/75% RH. Stability data of the developing site are sufficient to justify the claimed shelf life and storage conditions. Stability data (first three production batches) of the production site are awaited. Some trends are seen, but they remain within specification. For the powder a shelf life of 18 months when stored below 30°C is granted.
The shelf life has been changed by a type-IB variation into 3 years (NL/H/0958/001/IB/002). See also the table 'Steps taken after finalisation of the initial procedure' on Page 10.

An in-use stability study has been performed on constituted samples of batches used in the stability study on the powder. The following parameters were tested in in-use-stability studies: appearance, odour and taste of RFU suspension, suspensibility, resuspensibility, pH of RFU suspension, related substances and assay. No trends were observed during five days when stored at 25°C. Therefore, an in-use shelf life was granted of 5 days when stored below 25°C.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
No material of animal origin is used in the components of the powder. The starting material for azithromycin is made by fermentation as starting process, and the only starting material of animal origin, used in small amounts in the strain preservation for fermentation inoculum, is bacto-tryptone. This material, produced from a bovine milk derived casein, subsequently hydrolyzed by a protease of porcine origin, is in compliance with the EMEA NfG, as is the alternative skim milk. The milk powder is derived from milk, which is sourced from healthy animals fit for human consumption.

## II.2 Non clinical aspects

This product is a generic formulation of Zithromax, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

**Environmental risk assessment**
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of azithromycin released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

## II.3 Clinical aspects

Azithromycin monohydrate is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Azitromycine Mylan 200 mg/5 ml powder for oral suspension (Mylan B.V., the Netherlands) is compared with the pharmacokinetic profile of the British reference product Zithromax 200 mg/5 ml powder for suspension.

*The choice of the reference product*
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.

The formula and preparation of the bioequivalence batch differs slightly in composition from the commercial formulation. Trisodium phosphate dodecahydrate and flavouring agent cream caramel and has been used. It is shown that this does not influence the dissolution rate, and is therefore acceptable.

*Bioequivalence study*

A single center, open, randomised, two-way, crossover bioequivalence study was carried out under fasted conditions in 44 (+4 alternatives) healthy volunteers (22 males and 26 females), aged 18-46 years. Each subject received a single dose (500 mg) of one of the 2 azithromycin formulations. The suspension was administered with 240 ml water after a 10 h fasting period. For each subject there were 2 dosing periods, separated by a washout period of at least 21 days. Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 48, 72, 96, and 120 hours after administration of the products.

Two subjects were withdrawn during the washout period because of adverse events (head injury and erythema nodosum). Forty-four subjects were included in the statistical analysis. To balance the study, the last two subjects with the opposite treatment sequence were excluded from the pharmacokinetic and statistical analysis in compliance with the study protocol.

Azithromycin may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of azithromycin. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

The method of measuring plasma levels was validated and a validation report was provided. Statistical evaluation was performed for $C_{max}$, $AUC_{(0\text{-}t)}$, and $AUC_{(0\text{-}inf)}$ by ANOVA and the 90% confidence intervals for the ratio of test formulation over the reference formulation were calculated.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ (median, range)) of azithromycin under fasted conditions.

| **Treatment N=44** | **$AUC_{0\text{-}t}$** ng.h/ml | **$AUC_{0\text{-}\infty}$** ng.h/ml | **$C_{max}$** ng/ml | **$t_{max}$** h | **$t_{1/2}$** h |
|---|---|---|---|---|---|
| **Test** | 3743 ± 1231 | 4375 ± 1321 | 398 ± 147 | 2.0 (1.0 – 6.0) | 54 ± 14 |
| **Reference** | 3890 ± 1022 | 4571 ± 1145 | 415 ± 130 | 2.5 (1.0 – 4.0) | 54 ± 15 |
| ***Ratio (90% CI)** | 0.94 (0.88 - 1.01) | 0.94 (0.88 - 1.01) | 0.94 (0.85 - 1.03) | --- | --- |
| **CV (%)** | 17.9 | 16.8 | 26.1 | --- | --- |

**$AUC_{0\text{-}\infty}$** area under the plasma concentration-time curve from time zero to infinity
**$AUC_{0\text{-}t}$** area under the plasma concentration-time curve from time zero to t hours
**$C_{max}$** maximum plasma concentration
**$t_{max}$** time for maximum concentration
**$t_{1/2}$** half-life

**ln-transformed values*

The 90% confidence intervals calculated for $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$ and $C_{max}$ are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. A significant period effect was observed, however as it was considered that the difference between periods represents only a minor part of the total variance and therefore without clinical significance. Based on the pharmacokinetic parameters of azithromycin under fasted conditions, it can be concluded that Azitromycine Mylan and Zithromax are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk management plan
Azithromycin was first approved in 1991, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of azithromycin can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

**Product information**

SPC
The SmPC is greatly in line with the Azitromycine Merck tablets via the MRP with NL as RMS NL/H/546/01-02 as well as Azithromycin TEVA NL/H/614/01-02 and the FI/H/483. The table in section 5.1 has been updated to follow the recent guidelines as well as some minor differences in side effects section formulations.

During the MRP the SPCs, PILs and labelling texts for the procedures NL/H/0886/001-002/MR, NL/H/953-954/001-002/MR and NL/H/955-958/01/MR were harmonized.

Readability test
A readability test has not been performed, but reference is made to other user testing reports. These two reports have been provided with the PIL:

- FI/H/483/II/01: Azithromycin film-coated tablets for reference to most of the text, except for section 3 on the use of this other oral pharmaceutical form.
- UK/H/851-854: Cefpodoxime Proxetil 40 mg/5 ml powder for oral suspension for reference to the formulation on the use of the suspension.

A full justification is presented. The member states accept this waiver on the basis of the following:
The reference user test reports were accepted in recent MRP's. There were sufficient questions relevant for these azithromycin suspensions. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The patient information leaflet has been adapted sufficiently taking into account the results of the reference tests. A table of comparison of both azithromycin PIL texts has been provided to the RMS and was accepted as being comparable enough. The PIL still reflects the SPC of this oral suspension sufficiently.

## III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Azitromycine Mylan 200 mg/5 ml powder for oral suspension has a proven chemical-pharmaceutical quality and is a generic form of Zithromax 200 mg/5 ml powder for oral suspension. Zithromax is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is greatly in line with the SPCs of procedures NL/H/546/01-02, NL/H/614/01-02 and FI/H/483. Section 5.1 was updated. Braille conditions are met by the MAH.

The Board followed the advice of the assessors. Azithromycin Mylan powder for oral suspension was authorised in the Netherlands on 19 October 2006.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Azitromycine Mylan with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 1 March 2007.

A European harmonised birth date has been allocated 4 April 1991 and subsequently the first data lock point for azithromycin is April 2008. The first PSUR will cover the period from October 2006 to April 2008, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 28 February 2012.

The following post-approval commitments have been made during the procedure:

Product information
- The MAH committed to change the SPCs according to the decision of the CMD(h).
- In a next update of the SPC, in section 4.2 the MAH will change the sentence ‘To treat these patients tablets are also available’ into ‘To treat these patients other pharmaceutical forms are available’.
- The MAH committed to start a type II variation that section 5.1 will be adapted to EUCAST breakpoints whenever available.

Quality
- A commitment is made regarding the declaration of compliance to the revised standard NEN-ISO-8317:2003.
- The MAH commited to put the first three production batches of all dosage strengths on stability and to test according to the post-approval stability protocol as laid down.

## List of abbreviations

| | |
|---|---|
| ASMF | Active Substance Master File |
| ATC | Anatomical Therapeutic Chemical classification |
| AUC | Area Under the Curve |
| BP | British Pharmacopoeia |
| CEP | Certificate of Suitability to the monographs of the European Pharmacopoeia |
| CHMP | Committee for Medicinal Products for Human Use |
| CI | Confidence Interval |
| $C_{max}$ | Maximum plasma concentration |
| CMD(h) | Coordination group for Mutual recognition and Decentralised procedure for human medicinal products |
| CV | Coefficient of Variation |
| EDMF | European Drug Master File |
| EDQM | European Directorate for the Quality of Medicines |
| EU | European Union |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| GMP | Good Manufacturing Practice |
| ICH | International Conference of Harmonisation |
| MAH | Marketing Authorisation Holder |
| MEB | Medicines Evaluation Board in the Netherlands |
| OTC | Over The Counter (to be supplied without prescription) |
| PAR | Public Assessment Report |
| Ph.Eur. | European Pharmacopoeia |
| PIL | Package Leaflet |
| PSUR | Periodic Safety Update Report |
| SD | Standard Deviation |
| SPC | Summary of Product Characteristics |
| $t_{½}$ | Half-life |
| $t_{max}$ | Time for maximum concentration |
| TSE | Transmissible Spongiform Encephalopathy |
| USP | Pharmacopoeia in the United States |

## STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

| Scope | Procedure number | Type of modification | Date of start of the procedure | Date of end of the procedure | Approval/ non approval | Assessment report attached |
|---|---|---|---|---|---|---|
| Change in the name of the medicinal product in the Netherlands. | NL/H/0958/ 001/IB/001 | IB | 12-6-2007 | 13-7-2007 | Approval | N |
| Change in the shelf-life of the finished product as packaged for sale. Extention of the stability from 18 months to 36 months. | NL/H/0958/ 001/IB/002 | IB | 14-1-2008 | 13-2-2008 | Approval | N |
| Submission of an updated Ph. Eur. Certificate of Suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance. From a manufacturer currently approved. | NL/H/0958/ 001/IA/003 | IA | 14-4-2008 | 28-4-2008 | Approval | N |
| Change to batch release arrangements and quality control testing of the finished product. Replacement or addition of a manufacturer responsible for batch release, including batch control/testing | NL/H/0958/ 001/IA/004 | IA | 26-6-2008 | 10-7-2008 | Approval | N |
| Change to batch release arrangements and quality control testing of the finished product. Replacement or addition of a manufacturer responsible for batch release, including batch control/testing | NL/H/0958/ 001/IA/005 | IA | 4-8-2008 | 18-8-2008 | Approval | N |
| Repeat-use procedure with AT, BE, DE, EL, ES, FI, HU, MT, PL, PT, and SK. | NL/H/0958/ 001/E/001 | E | 29-1-2009 | 29-4-2009 | Approval | Y, Annex I |
| Change in the name of the medicinal product in Italy. | NL/H/0958/ 001/IB/006 | IB | 21-7-2009 | 20-8-2009 | Approval | N |

## Annex I - Repeat use procedure (NL/H/0958/001/E/001)

The Repeat use procedure started on 21 January 2009. There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states (AT, BE, DE, EL, ES, FI, HU, MT, PL, PT, SK), on the basis of the data submitted, considered that essential similarity has been demonstrated between the test powder for oral suspension 200 mg/ 5 ml (Novartis, India) and the reference powder for oral suspension 200 mg/ 5 ml (Pfizer, UK), and have therefore granted a marketing authorisation. The repeat use procedure was finished on 29 April 2009.

The date for the first renewal was allocated based on day 90 of the MRP: 28 February 2012.

A European harmonised birth date has been allocated 1991/04/04 with first data lock point being 2011/04. The PSUR submission cyclus is 3 years.

The following post-approval commitments have been made during the procedure:

**Quality**

1. Reference is made to the CoS. A commitment is made to state the standards and materials used for the applicants own tests.

2. A commitment is made to provide additional information on the flavouring agent cream caramel. Since a flavouring substance is a complex mixture the composition of the flavouring substance should be included unambiguously.
   Two options are available:
   - Inclusion of the quantitative composition of all components.
   - Inclusion of the qualitative composition of all components, accompanied by additional information on the consistency of the composition, e.g. GC-chromatogram. Also, an identification test for cream caramel should be provided and information on the carrier material of the flavouring agent should be included.

3. A commitment is made to submit the specifications (release and shelf life) containing the harmonized category for microbial limits of the finished product and harmonized microbial methods to the authorities as a quality variation immediately after the closure of this procedure.

**Product Information (SmPC/PIL/Labelling)**

4. As per Germany's Day 75 comments, an SmPC/PIL/Labelling commitment has been made to submit a type II variation after closure of procedure to include the following warning regarding the indication of “skin and soft tissue infections":
   “The main causative agent of soft tissue infections, Staphylococcus aureus, is frequently resistant to azithromycin. Therefore, susceptibility testing is considered a precondition for treatment of soft tissue infections with azithromycin.”

5. As per Portugal’s Day 50 comments, a SmPC/PIL commitment has been made to include the necessary general statements for the possible environmental risk impact during the earliest variation in which the product information is adapted.