PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Azitromycine Apotex 250 mg and 500 mg film-coated tablets
Apotex Europe BV, the Netherlands

azithromycin (as dihydrate)

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/1298/001-002/DC
Registration number in the Netherlands: RVG 101499,101500

25 January 2010

Pharmacotherapeutic group: antibacterials for systemic use, macrolids
ATC code: J01FA10
Route of administration: oral
Therapeutic indication: the following bacterial infections induced by micro-organisms susceptible to azithromycin: lower respiratory tract infections (acute bronchitis and mild to moderate community-acquired pneumonia), upper respiratory tract infections (sinusitis and pharyngitis/tonsillitis), infections of the skin and soft tissues of mild to moderate severity, acute otitis media, uncomplicated Chlamydia trachomatis urethritis and cervicitis.

Prescription status: prescription only
Date of authorisation in NL: 10 July 2009
Concerned Member States: Decentralised procedure with BE, IT, CZ (500 mg only), PL (500 mg only)
Application type/legal basis: Directive 2001/83/EC, Article 10(1)

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 Apotex 250 mg and 500 mg film-coated tablets, from Apotex Europe BV. The date of authorisation was on 10 July 2009 in the Netherlands.

The product is indicated for the following bacterial infections induced by micro-organisms susceptible to azithromycin:
- infections of the lower respiratory tract: acute bronchitis and mild to moderate community-acquired pneumonia;
- infections of the upper respiratory tract: sinusitis and pharyngitis/tonsillitis;
- acute otitis media;
- infections of the skin and soft tissues of mild to moderate severity e.g. folliculitis, cellulites, erysipelas;
- uncomplicated Chlamydia trachomatis urethritis and cervicitis.

Consideration should be given to official guidance on the appropriate use of antibacterial agents. Azithromycin is not the first choice for the empiric treatment of infections in areas where the prevalence of resistant isolates is 10% or more.

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 decentralised procedure concerns a generic application claiming essential similarity with the innovator products Zithromax 250 mg and 500 mg tablets (NL License RVG 19432 and 19433 respectively) which have been registered in the Netherlands by Pfizer B.V. since 1997. In addition, reference is made to Zithromax authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

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 500 mg tablets, registered in the Netherlands. 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. No paediatric development programme has been submitted, as this is not required for generics.
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 dihydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white to off-white powder, which is practically insoluble in water, freely soluble in anhydrous ethanol and in methylene chloride. Azithromycin exhibits polymorphism. There are two polymorphic forms of azithromycin. The active substance as the B form.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacture
The manufacturing process consists of three stages, which have been sufficiently described.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur, with additional requirements for residual solvents. The specifications are acceptable in view of the route of synthesis and the various European guidelines. An XRD (X-ray Diffraction) test for solid phase identification is included to ensure and control polymorphism. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three commercial scaled batches.

Stability of drug substance
Stability data on the active substance have been provided for three full scaled batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The batches were adequately stored. The drug substance remained stable under accelerated and long term conditions. Based on the data submitted, a re-test period of 24 months was granted, without specific storage conditions

* Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Medicinal Product

Composition
The film-coated tablets appear as follows:
Azithromycin Apotex 250 mg film-coated tablets - white, oval, biconvex, with ‘APO’ engraved on one side and ‘AZ250’ on the other.
Azithromycin Apotex 500 mg film-coated tablets - white, oval, biconvex, with ‘APO’ engraved on one side and ‘AZ500’ on the other.

The film-coated tablets are packed in white opaque, PVC/aluminium foil blisters, containing 2, 3, 4, 6 or 30 tablets, and in white, round HDPE bottles with a blue PP Lift N Peel cap closure containing 2, 3, 4, 6 or 30 tablets.
The excipients are:

*Tablet core* - calcium hydrogen phosphate dihydrate, hydroxypropyl cellulose (E643), croscarmellose sodium, and magnesium stearate (E572).

*Tablet coating* - hypromellose (E464), lactose monohydrate, titanium dioxide (E171), triacetin.

The two tablet formulations are fully dose proportional. All excipients are well known and the quantities used are common for immediate release tablets. The excipients comply with the Ph.Eur.

**Pharmaceutical development**

The development of the product has been described, the choice of excipients is justified and their functions explained. The formulation development was undertaken on the basis of the study of the innovator product and review of literature concerning the physicochemical characterisation of the active ingredient and the excipients used. A bioequivalence study was carried out using the 500 mg Azithromycin dihydrate tablet of the applicant and Zithromax 500 mg tablets of the innovator. The dissolution profiles of the bio-batch manufactured by the MAH and Zithromax are considered to be comparable. Moreover, the comparative dissolution data of the Azithromycin film-coated tablets with the reference products from several member states show that the pivotal batches exhibit dissolution profiles which are similar to the respective reference products (from the Netherlands, Germany, Sweden, Poland, Italy and Czech Republic) and to the biobatch. The pharmaceutical development has been adequately performed.

**Manufacturing process**

Azithromycin dihydrate tablets are manufactured by dry granulation. A description of the manufacturing process, process controls, and a flow chart are included. Process validation studies have been conducted on the pivotal batches of Azithromycin tablets 250 mg and 500 mg. The separate steps of the manufacturing process are adequately validated and the values for the various in-process controls comply with the specifications.

**Quality control of drug product**

The product specification includes tests for description, identification (UV, HPLC), disintegration test, resistance crushing, dissolution, related compounds, uniformity of dosage units, assay and microbial contamination. Release and shelf-life limits are identical. The analytical methods have been adequately described and validated. For both strengths, batch analytical data have been provided on three pilot-scale batches. All batches comply with the specifications.

**Stability tests on the finished product**

For both strengths stability data on the drug product have been provided for three pilot-scale batches stored at 25°C/60% RH (24 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are in accordance with the ICH stability guideline. The batches were stored in PVC/Alu blisters and HDPE containers. For none of the batches tested a trend or change was observed. In line with these results, no special storage conditions are required. The proposed shelf-life of 24 months is acceptable. The photostability testing is performed in accordance with the Note for Guidance on the stability testing of new active substances and finished products. From the photostability testing it can be concluded that the drug product is not susceptible to light.

The MAH has committed to put the first three commercial batches on long term stability studies through the proposed shelf-life and on accelerated studies for 6 months. Moreover, the MAH has committed to perform the uniformity of dosage units for future batches as per the release specification.

**In-use stability**

In-use stability data have been provided for the 30’s and 500’s HDPE bottle packaging over 30 days of use. In view of these results, a specific in-use shelf-life is not required for the 30’s HDPE bottle packaging. The 500’s HDPE bottle packaging was not proposed for this application.
Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

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

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Azitromycine Apotex 500 mg film-coated tablets (Apotex Europe BV, the Netherlands) was compared with the pharmacokinetic profile of the reference product Zithromax 500 mg tablets (Pfizer, the Netherlands).

From this study, pharmacokinetic summary data and data of the statistical analysis were submitted for 56 subjects. The MAH considered one subject as an outlier, based upon statistical analysis of the data. These were not included in the pharmacokinetics variables and the statistical analysis. According to the CPMP guideline “Note for guidance on the investigation of bioavailability and bioequivalence” (CPMP/EWP/QWP/1401/98), and the Question and Answer document, exclusion of subjects can only be based on nonstatistical reasons, like vomiting or diarrhoea, and therefore the member states raised a major objection. The MAH was requested to submit the outcome of the statistical analysis for this outlier.

The requested data analysis including the data for the outlier was performed by the MAH and results were discussed in detail. Since apparent clinical or bioanalytical events could not be identified to explain the cause of the aberrant values for the outlier, the member states judged that the bioequivalence study failed to demonstrate bioequivalence of both the test and the reference product.

Consequently, the MAH repeated the bioequivalence study. The setup and results of this second study are discussed below.

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 (if applicable) in different member states.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Study design
A single-dose, randomised, two-way cross-over bioequivalence study was carried out under fasted conditions in 76 healthy male volunteers, aged 18 - 45 years. Each subject received a single dose (500 mg) of one of the 2 azithromycin formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. Fasting was continued for 4 hours after dosing. For each subject there were 2 dosing periods, separated by a washout period of 28 days.
Blood samples were collected pre-dose and at 0.5, 1, 1.33, 1.66, 2, 2.33, 2.66, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72, 96, and 120 hours after administration of the products. The analytical method is adequate validated and considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable. 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.

Results

One subject was withdrawn in Period I due to vomiting. Four subjects did not check in for Period II. One subject tested positive for alcohol during Period II check in. Two subjects were withdrawn due to adverse events. Sixty-eight subjects completed the study entirely and were eligible for pharmacokinetic analysis.

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

<table>
<thead>
<tr>
<th>Treatment N=68</th>
<th>$\text{AUC}_{0-t}$</th>
<th>$\text{AUC}_{0-\infty}$</th>
<th>$C_{\text{max}}$</th>
<th>$t_{\text{max}}$</th>
<th>$t_{1/2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>4121 ± 959</td>
<td>4707 ± 1093</td>
<td>517 ± 188</td>
<td>2.6 ± 0.8</td>
<td>48 ± 6</td>
</tr>
<tr>
<td>Reference</td>
<td>4225 ± 1039</td>
<td>4816 ± 1185</td>
<td>517 ± 187</td>
<td>2.5 ± 0.7</td>
<td>48 ± 6</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>0.98 (0.93 – 1.03)</td>
<td>0.98 (0.93 – 1.03)</td>
<td>0.99 (0.92 – 1.06)</td>
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<tr>
<td>CV (%)</td>
<td>18.6</td>
<td>18.5</td>
<td>26.3</td>
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</table>

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

*In-transformed values

The 90% confidence intervals calculated for $\text{AUC}_{0-t}$, $\text{AUC}_{0-\infty}$ and $C_{\text{max}}$ are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of azithromycin under fasted conditions, it can be concluded that Azithromycin Apotex 500 mg film-coated tablets and Zithromax 500 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Extrapolation of results

The 500 mg film-coated tablets are dose proportional with the 250 mg film-coated tablets. The manufacturing process is the same by the same manufacturer. Moreover, the pharmacokinetics of azithromycin are linear over the dose range of 250 to 1000 mg. The results of the bioequivalence study performed with the 500 mg film-coated tablets therefore apply to the 250 mg strength.

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 post-authorisation 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

Readability test
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. Testing was performed with in total 20 participants. Ten participants were included in each of the two rounds of user testing. The recruitment methods and individual demographic and sociologic details were provided in the final report.

A total of 14 questions have been evaluated with regard to findability, ease of understanding and subjective impression of the PIL by the participants. The responses were recorded satisfactorily. The user test showed that the leaflet enabled more than of the 90% of participants to find the information and more than 90% of those understood the information good or in detail.

The main objectives of the user testing have been achieved and the conclusion of the MAH is accurate. Furthermore the overall impression of the methodology and the overall impression of the leaflet structure are positive. The readability test has been sufficiently performed.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Azithromycine Apotex 250 mg and 500 mg film-coated tablets have a proven chemical-pharmaceutical quality and are a generic form of Zithromax 250 mg and 500 mg tablets. Zithromax is a well-known medicinal product with an established favourable efficacy and safety profile.

The initial bioequivalence study as submitted by the MAH was rejected by the member states, because aberrant values for one subject were not included in the pharmacokinetic variables and the statistical analysis. Apparent clinical or bioanalytical events as a cause of this outlier could not be identified and consequently, the MAH repeated the bioequivalence study. For this second bioequivalence study, 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 consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other azithromycin containing products.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Azithromycine Apotex film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 10 June 2009. Azithromycine Apotex 250 mg and 500 mg film-coated tablets were authorised in the Netherlands on 10 July 2009.

A European harmonised birth date has been allocated (4 April 1991) and subsequently the first data lock point for azithromycin is April 2011. The first PSUR will cover the period from June 2009 to April 2011, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 30 December 2011.

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

Quality - medicinal product
- The MAH has committed to put the first three commercial batches on long term stability studies through the proposed shelf-life and on accelerated studies for 6 months.
- The MAH has committed to perform the uniformity of dosage units for future batches as per the release specification. Test on uniformity of dosage units shall be carried out ‘as per Ph. Eur.’ by mass variation using 10 tablets. Tests on uniformity of dosage units can not be performed retrospectively with the current batches due to non availability of the samples.

Quality - active substance
- Three commitments were made by the manufacturer of the active substance.
**List of abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ASMF</td>
<td>Active Substance Master File</td>
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<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical classification</td>
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<td>AUC</td>
<td>Area Under the Curve</td>
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<td>BP</td>
<td>British Pharmacopoeia</td>
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<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
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<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
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<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>C\text{max}</td>
<td>Maximum plasma concentration</td>
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<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
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<tr>
<td>CV</td>
<td>Coefficient of Variation</td>
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<td>EDMF</td>
<td>European Drug Master File</td>
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<td>EDQM</td>
<td>European Directorate for the Quality of Medicines</td>
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<td>EU</td>
<td>European Union</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>GLP</td>
<td>Good Laboratory Practice</td>
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<td>GMP</td>
<td>Good Manufacturing Practice</td>
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<td>ICH</td>
<td>International Conference of Harmonisation</td>
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<td>MAH</td>
<td>Marketing Authorisation Holder</td>
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<td>MEB</td>
<td>Medicines Evaluation Board in the Netherlands</td>
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<tr>
<td>OTC</td>
<td>Over The Counter (to be supplied without prescription)</td>
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<tr>
<td>PAR</td>
<td>Public Assessment Report</td>
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<tr>
<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
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<tr>
<td>PIL</td>
<td>Package Leaflet</td>
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<tr>
<td>PSUR</td>
<td>Periodic Safety Update Report</td>
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<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>t\text{½}</td>
<td>Half-life</td>
</tr>
<tr>
<td>t\text{max}</td>
<td>Time for maximum concentration</td>
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<tr>
<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
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<tr>
<td>USP</td>
<td>Pharmacopoeia in the United States</td>
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<tr>
<td>XRD</td>
<td>X-ray Diffraction</td>
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<td>Scope</td>
<td>Procedure number</td>
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<td>----------------------------------------------------------------------</td>
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<td>Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Secondary packaging site for all types of pharmaceutical forms.</td>
<td>NL/H/1298/001-002/IA/001</td>
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</tbody>
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