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

# Olanzapine Nyzol 15 mg and 20 mg film-coated tablets Laboratorios Lesvi, Spain

# olanzapine

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/1043/005-006/DC**
**Registration number in the Netherlands: RVG 103398,103399**

**16 March 2010**

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|---|---|
| Pharmacotherapeutic group: | antipsychotics; diazepines, oxazepines, thiazepines, and oxepines |
| ATC code: | N05AH03 |
| Route of administration: | oral |
| Therapeutic indication: | schizophrenia; moderate to severe manic episode; maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response; moderate to severe manic episode; prevention of recurrence in patients with bipolar disorder in patients whose manic episode has responded to olanzapine treatment |
| Prescription status: | prescription only |
| Date of authorisation in NL: | 17 September 2009 |
| Concerned Member States: | Decentralised procedure with BG, CZ, DE, EL, HU, RO, SK, and UK |
| 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 Olanzapine Nyzol 15 mg and 20 mg film-coated tablets from Laboratorios Lesvi. The date of authorisation was on 17 September 2009 in the Netherlands. The product is indicated for:

- treatment of schizophrenia
- maintenance of clinical improvement during continuation therapy in patients who have shown an initial treatment response.
- treatment of moderate to severe manic episodes.
- prevention of recurrence in patients with bipolar disorder in patients whose manic episode has responded to olanzapine treatment

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

Olanzapine is an antipsychotic, antimanic and mood stabilising agent that demonstrates a broad pharmacologic profile across a number of receptor systems. Olanzapine is a member of the so-called atypical antipsychotics, as opposed to the classical antipsychotics, such as haloperidol, showing greater affinity to Serotonin 5HT2A-receptors than to Dopamine D2-receptors. Atypical antipsychotics would elicit fewer extra pyramidal symptoms and would have an effect on the negative symptoms of the disease.
In preclinical studies, olanzapine exhibited a range of receptor affinities (Ki; < 100 nM) for serotonin 5-HT2A/2C, 5-HT3, 5-HT6; dopamine D1, D2, D3, D4, D5; cholinergic muscarinic receptors m1-m5; α-1 adrenergic; and histamine H1 receptors. Animal behavioural studies with olanzapine indicated 5HT, dopamine, and cholinergic antagonism, consistent with the receptor-binding profile. Olanzapine demonstrated a greater in-vitro affinity for serotonin 5-HT2 than dopamine D2 receptors and greater 5-HT2 than D2 activity in vivo, models. Electrophysiological studies demonstrated that olanzapine selectively reduced the firing of mesolimbic (A10) dopaminergic neurons, while having little effect on the striatal (A9) pathways involved in motor function. Olanzapine reduced a conditioned avoidance response, a test indicative of antipsychotic activity, at doses below those producing catalepsy, an effect indicative of motor side-effects. Unlike some other antipsychotic agents, olanzapine increases responding in an “anxiolytic” test.

The efficacy and safety of olanzapine has been demonstrated in randomised, placebo-controlled and comparative trials in positive and negative symptoms of schizophrenia, and also as monotherapy or in combination with mood stabilizers in the treatment of acute manic or mixed episodes associated with bipolar disorder. A summary of these studies may be found in the EPAR of Zyprexa to be found on website of the EMA (http://www.ema.europa.eu/humandocs/PDFs/EPAR/olanzapine_mylan/H-961-en6.pdf).

This decentralised procedure concerns a generic application claiming essential similarity with Zyprexa 15 mg and 20 mg coated tablets ((EU License EU/1/96/022) which have been registered through a centralised procedure by Eli Lilly since 2000.
The strengths applied for (15 mg and 20 mg), are line-extensions of the 2.5, 5, 7.5 and 10 mg Olanzapine film-coated tablets which were approved via a decentralised procedure on 12 January 2008.

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 Zyprexa 10 mg film-coated tablets, from the Spanish market. 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, as this is not required for generic medicinal products.

# 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 olanzapine, an established active substance, however not described in the European Pharmacopoeia (Ph.Eur.*) or any other pharmacopoeia. The drug substance is a yellow to light yellow crystalline powder. It is soluble in methylene chloride, acetone and tetrahydrofuran; freely soluble in acetonitrile, glacial acetic acid and in acid aqueous solutions; slightly soluble in methanol; and practically insoluble in water and in basic aqueous solutions.

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.

Manufacturing process
A flow diagram of the manufacturing process, including in-process controls has been provided. The chemical-pharmaceutical documentation and Expert Report in relation to olanzapine are of sufficient quality in view of the present European regulatory requirements.

Quality control of drug substance
The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for 3 production-scale batches. Polymorphism is tested by X-ray powder diffraction and IR. It was confirmed that the active pharmaceutical substance used corresponds to that of polymorphic form I.

Stability of drug substance
Stability data on the active substance(s) have been provided for 3 batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are in accordance with the ICH stability guideline. No trends or out of specification results have been observed for the parameters investigated.
Olanzapine is mainly degraded in basic, oxidative and light conditions. Light testing on solid stressed samples shows a moderate degradation without changes in physical properties. Light testing for Olanzapine solution sample showed changes in physical properties and significant photolytic degradants were detected in the stressed samples concluding that Olanzapine is light sensitive. Olanzapine was slightly degraded in acidic and thermal conditions.
Based on the study results, suitability of the proposed analytical procedures to identify degradations products was demonstrated.

Based on the data submitted, a retest period could be granted of 2 years when '*stored in the original packaging, protected from air, light and heat*'.
The MAH has committed to submit stability data until the end of the retest period when available.

** 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
Olanzapine Nyzol 15 mg and 20 mg film-coated tablets contain as active substance 15 mg and 20 mg of olanzapine respectively, and appear as follows:
*15 mg* - blue oblong, 14.9 – 17.1 mm major diameter, 6.5 – 7.5 mm minor diameter, biconvex tablets with the inscription "15" debossed in one side.
*20 mg* - pink oblong, 15.8 – 18.2 mm major diameter, 7.9 – 9.1 mm minor diameter, biconvex tablets with the inscription "20" debossed in one side.

The film-coated tablets are packed in PA/Al/PVC/Al blisters, 28, 35, 56 or 70 tablets per carton.

The excipients are:
*Tablet core* - lactose monohydrate, microcrystalline cellulose E-460, low-substituted hydroxypropyl, cellulose E-463, crospovidone, colloidal anhydrous silica, magnesium stearate E-470.
*Tablet coat (15 mg)* - polyvinyl alcohol, titanium dioxide E-171, talc, soya lecithin E-322, xanthan gum E-415, indigo carmine E-132.
*Tablet coat (20 mg)* - polyvinyl alcohol, titanium dioxide E-171, talc, soya lecithin E-322, xanthan gum E-415, iron oxide red E-172.

The contents of the two tablet formulations are dose proportional.

Pharmaceutical development
The composition of the additional strengths is exactly the same as the approved ones, except for two minority colouring agents (aesthetic function) of the coating agents. The nominal mass of the coated tablets increases proportionally to strength (558 and 744 mg).
The development of the product has been described, the choice of excipients is justified and their functions explained. The packaging materials are usual and suitable for the product at issue.
Olanzapine can be classified as a non-hygroscopic product.
The final formulation is based on a diluents study. Based on all the results a defined mixture of lactose monohydrate and microcrystalline cellulose is selected as the diluent for the formulation, since this mixture provides the optimum pharmacotechnical characteristics to the tablets and no problems have been observed in the two stability studies performed with this formulation.
Comparative dissolution profiles of each strength to the corresponding related brand leader product Zyprexa have been provided. Based on the similarity of the dissolution profiles in the different media tested and in accordance to the FDA (Food and Drug Administration) recommended dissolution method for olanzapine tablets, 0.1 M hydrochloric acid is selected as the dissolution medium for all strengths of Olanzapine film-coated tablets. The dissolution profiles were accepted as similar without further mathematical evaluation, as in all cases more than 85% of the drug dissolved within 15 minutes.

Excipients
The specifications of lactose monohydrate, cellulose microcrystalline, crospovidone, colloidal anhydrous silica, magnesium stearate and purified water are in accordance with the Ph. Eur. The specification of low-substituted hydroypropyl cellulose is in accordance with the USP*. Certificates of analysis showing compliance with the specification, have been submitted for all excipients used. An acceptable in-house specification for Opadry AMB Blue 80W30580 and Opadry AMB Pink 80W34300 were provided.

Manufacturing process
A flow diagram of the manufacturing process, including in process controls was provided. The manufacturing process consists of mixing of the constituents followed by direct compression and packaging. Process validation data on the product have been presented for 2 batches in accordance with the relevant European guidelines.
The MAH has committed to validate the manufacturing process in three routine production scale batches for each strength, and to submit the results when available.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, average mass, uniformity of dosage units, loss on drying, dissolution, identification, assay, impurities, and microbial contamination. 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 analytical data for 3 batches from the proposed production site(s) have been provided, demonstrating compliance with the specification. No degradation products have been observed at level higher than 0.05% at release. During the stability studies a small increase of two specific impurities was observed. Both impurities are described in the manufacturer DMF. Other degradation products have been detected, but at levels not more than 0.1% (reporting threshold).
The MAH has committed to submit Certificates of Analysis for three subsequent production batches of all strengths of the medicinal product, containing results of tests for microbial purity.

Stability tests on the finished product
Stability data on the product have been provided for three batches of each strength. The batches were stored at 25°C/60% RH and 40°C/75% RH for 24, 18, and 6 months. The conditions used in the stability studies are in accordance with the ICH stability guideline. On basis of the data submitted, a shelf life was granted of 2 years. The labelled storage conditions are 'store in the original package to protect from moisture'.
The MAH has committed to continue the long term stability studies through the proposed shelf life period and to report updates as they become available. Moreover, The MAH committed to place the next production batch from one manufacturer on long term and accelerated stability studies. In addition, one production batch per year will be placed on long term stability studies.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The only excipient of the formula of animal origin is lactose monohydrate. A declaration is that the milk is sourced from healthy animals in the same conditions as milk collected for human consumption and the lactose is prepared without the use of other ruminant materials than calf rennet was provided. The sourcing of the milk is in compliance with Directive 92/46/EEC. The excipient magnesiumstearate is of vegetable origin.

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

## II.2 Non clinical aspects

These products are generic formulations of Zyprexa film-coated tablets, which are 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 products are 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 olanzapine 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

Olanzapine 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 Olanzapine Nyzol 10 mg film-coated tablets (Laboratorios Lesvi, Spain) is compared with the pharmacokinetic profile of the reference product Zyprexa 10 mg film-coated tablets (Eli Lilly, the Netherlands).

*The choice of the reference product*
Zyprexa tablets are registered via the centralised procedure and hence are presumed to be identical in all member states of the EEA. The formula and preparation of the bioequivalence batches is identical to the formula proposed for marketing.

*Study design*
A single-dose, open, cross-over bioequivalence study was carried out under fasted conditions in 23 (12 male, 11 female) healthy, non-smoking volunteers.. Each subject received a single dose (10 mg) of one of the 2 olanzapine formulations. The tablets were orally administered with 200 ml water after an overnight fast. Fasting was continued for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of at least three weeks. Blood samples were collected pre-dose and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 18, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216 and 240 hours after administration of the products.

*Analytical / statistical methods*
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.

Olanzapine may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of olanzapine. 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*
During the washout period, just before period 2 of the study began, 2 subjects dropped out of the study (1 man and 1 woman) for personal reasons. Since one of the subjects standing in for one of the drop-outs might also have had to drop out midway through the study, the decision was taken to include one more volunteer and to begin the experimental period. Since 20 subjects had completed the study, which was the sample size established in the protocol, this last volunteer was withdrawn from the study after completing period I. Twenty subjects were eligible for pharmacokinetic analysis.

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

| **Treatment N = 20** | **$AUC_{0-t}$** ng.h/ml | **$AUC_{0-\infty}$** ng.h/ml | **$C_{max}$** ng/ml | **$t_{max}$** h | **$t_{1/2}$** h |
|---|---|---|---|---|---|
| **Test** | 967.8 (276.5) | 988.1 (288.1) | 30.7 (7.4) | 4 (1-5) | --- |
| **Reference** | 890.7 (265.0) | 913.3 (282.7) | 30.0 (6.1) | 4 (3-7) | --- |
| **Ratio (90% CI)* | 1.09 (1.00 – 1.19) | 1.09 (1.00 – 1.19) | 1.10 (1.04 – 1.16) | --- | --- |
| *CV (%)* | 16% | 16% | 10.4% | --- | --- |

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| **$AUC_{0-\infty}$** | area under the plasma concentration-time curve from time zero to infinity |
| **$AUC_{0-t}$** | 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 $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{max}$ are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of olanzapine under fasted conditions, it can be concluded that Olanzapine Nyzol 10 mg film-coated tablets and Zyprexa 10 mg coated 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 15 mg and 20 mg tablets are dose-proportional with the 10 mg tablet. The tablets have been manufactured by the same manufacturing process. In addition, olanzapine shows linear pharmacokinetics. The results of the bioequivalence study performed with the 10 mg film coated-tablets therefore apply to the other strengths.

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
The MAH committed to follow the Risk Management Plan of the innovator, where appropriate. This means that the MAH committed to the following issues:

- The PSUR cycle of the innovator, Zyprexa, will be adhered to, which currently is a yearly cycle with data lock point of 31 March.
- The following issues will be monitored and specifically reported upon in the PSURs:
  - In all patients (including paediatric patients): Weight gain, glucose dysregulation, dyslipidaemia, adverse pregnancy outcomes, including gestational diabetes, bradycardia with serious outcome, convulsions (seizures where initial report does not specify presence/absence of other risk factors), eosinophilia with serious outcome, haematological effects, hepatic effects, hyperglycaemia/diabetes mellitus/ketoacidosis, hypertriglyceridaemia/hyperlipidaemia, hypotension, overdose of olanzapine alone (and where either the patient died, or survival after olanzapine overdose > 200 mg or olanzapine plasma concentration > 200 ng/ml), pancreatitis, QT interval prolongation, respiratory depression/hypoventilation/apnoea, sinus pause, sudden death, thromboembolic events, withdrawal symptoms (including infants) and medication errors.
  - In paediatric patients only: sedation, hepatic-related events and hyperprolactinaemia and pituitary enlargement
- The SPC for the product will follow and be kept in line with that of the innovator.
- The MAH will follow, where appropriate, the risk minimisation activities of the innovator, e.g. participate in DHPCs where needed, produce and distribute educational material for patients and physicians when applicable, etc.

**Product information**

SPC
Zyprexa has been authorised through the centralised procedure in the EU, and thus, harmonised product information exists within the EU. The SPC proposed for the Olanzapine 15 and 20 mg strengths is in accordance with the current version of the SPC for Zyprexa and will be kept in line with that of the innovator product.

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. The test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. After each round the results were evaluated to determine whether the pre-set criteria were met, and to amend the package leaflet if required. The study included a personal interview. The questions were asked verbally, and the interviewer was instructed to note the answers in detail and see how the interviewed subject manages the leaflet and looks for information in it. The interviewers were instructed to ask the participant to explain the information found in their own words. Any comments or suggestions should be noted. The interviewer was not allowed to help the participants to find the answers or to give clues to find the answer. The interviewers were allowed to repeat the question in a more informal way or using more friendly terms. Information on the background of the interviewers has been provided. A few, mainly linguistic, changes were made after the first test round. Overall, each and every question met criterion of 81% correct answers. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been sufficiently performed.

## III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Olanzapine Nyzol 15 mg and 20 mg film-coated tablets have a proven chemical-pharmaceutical quality and are a generic forms of Zyprexa 15 mg and 20 mg -coated tablets. Zyprexa 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 consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

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 Olanzapine Nyzol 15 mg and 20 mg mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 12 July 2009. Olanzapine Nyzol was authorised in the Netherlands on 17 September 2009.

The MAH will follow the PSUR submission cycle as agreed for the innovator product Zyprexa, which at the time of registration was a yearly cycle with data lock point of 31 March.

The date for the first renewal will be: 12 January 2013

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

Quality - active substance
- The MAH has committed to submit stability data until the en of the retest period when available.

Quality - medicinal product
- The MAH has committed to validate the manufacturing process in three routine production scale batches for each strength, and to submit the results when available.
- The MAH has committed to submit Certificates of Analysis for three subsequent production batches of all strengths of the medicinal product, containing results of tests for microbial purity.
- The MAH has committed to continue the long term stability studies through the proposed shelf-life period and to report updates as they become available.
- The MAH committed to place the next production batch from one manufacturer on long term and accelerated stability studies. Moreover, one production batch per year will be placed on long term stability studies.

## List of abbreviations

| | |
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| 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 |
| FDA | Food and Drug Administration |
| 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 |
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