COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Metformin hydrochloride ELC 500 mg and 750 mg prolonged-release tablets (metformin hydrochloride)

NL/H/4764/001-002/DC

Date: 13 September 2021

This module reflects the scientific discussion for the approval of Metformin hydrochloride ELC 500 mg and 750 mg prolonged-release tablets. The procedure was finalised at 17 March 2021. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ERP	European Reference Product
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Metformin hydrochloride ELC 500 mg and 750 mg prolonged-release tablets, from ELC GROUP s.r.o. The application for the 1000 mg prolonged-release tablets was withdrawn during the procedure.

The products are indicated for:
Treatment of type 2 diabetes mellitus in adults, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control. Metformin Hydrochloride Prolonged-release Tablets may be used as monotherapy or in combination with other oral antidiabetic agents, or with insulin.

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

This decentralised procedure concerns a generic application claiming essential similarity with the European Reference Products (ERP) Glucophage XR, 500 mg and 750 mg prolonged-release tablets of Merck Sante s.a.s., authorised in Poland since 17 May 2006 (500 mg) and 3 March 2009 (750 mg). In the bioequivalence studies medicinal products from the United Kingdom were used, which are similar to the innovator products.

The concerned member states (CMS) involved in this procedure were Italy and Poland.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Metformin hydrochloride ELC 500 mg prolonged-release tablets is a white to off-white capsule shaped, 18 mm in length, 9 mm in width and 6 mm in thickness, biconvex, bevelled edge tablet, with occasionally mottled appearance, debossed with "ℸL001" on one side and plain on the other side.

Metformin hydrochloride ELC 750 mg prolonged-release tablets is a white to off-white capsule shaped, 18 mm in length, 9 mm in width and 7.3 mm in thickness, biconvex, uncoated tablet and plain on both faces.

The prolonged-release tablets contain as active substance 500 mg and 750 mg of metformin hydrochloride, respectively.

The pharmaceutical forms of both strengths are packed in plain aluminium foil/PVC/PVDC foil blister packs.

The excipients are:
500 mg tablets - magnesium stearate, carmellose sodium and hypromellose.

750 mg tablets - magnesium stearate, methacrylic acid – ethyl acrylate copolymer (1:1) dispersion 30%, macrogol, povidone, carmellose sodium and hypromellose.

II.2 Drug Substance

The active substance is metformin hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Metformin hydrochloride is a white or almost white crystalline powder and is freely soluble in water, slightly soluble in ethanol (96%) and practically insoluble in acetone and methylene chloride. The active substance shows polymorphism and is manufactured as the stable polymorphic form A.

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 suitability 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 general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and of additional tests for residual solvents, bulk density, particle size distribution and nitrosamine impurities. The specification is acceptable. Batch analytical data demonstrating compliance with the drug substance specification have been provided for four batches.

Stability of drug substance
Stability data on the active substance have been provided for batches from two manufacturing sites of the same manufacturer (twelve batches from one location, nine from the other location). The batches were stored at 25°C/60% RH (up to 72 months) and 40°C/75% RH (six months). The batches were stored in double low density polyethylene (LDPE) or high density, high molecular high density polyethylene (HMHDPE) bags in a secondary box or drum. The stability data showed no clear changes or trends in any of the tested parameters at both long-term and accelerated storage conditions. The results were

the same for both manufacturing sites and both packaging configurations. The claimed retest period of three years with storage condition 'Store below 25°C' is justified.

II.3 Medicinal Products

Pharmaceutical development

The products are established pharmaceutical forms and their development is adequately described in accordance with relevant European guidelines. The choice of excipients is justified and their functions are explained.

The main development studies described in the dossier were the characterisation of the reference products, formulation optimisation studies, dissolution method development and the performance of comparative dissolution studies. Bioequivalence studies have been performed for both product strengths versus their respective reference product strengths. The drug product batches used in the bioequivalence studies are representative batches that were manufactured according to the finalised composition and manufacturing process. In support of the bioequivalence studies, comparative dissolution studies were performed between the respective test and reference batches used in the bioequivalence studies. These showed similar dissolution profiles within the physiological pH range (three pH's). The choices of the packaging and manufacturing process are justified. The pharmaceutical development of the products has been adequately performed.

Manufacturing process

The main steps of the manufacturing process are the mixing of intragranular components, binder suspension/solution preparation, wet granulation, drying, blending, lubrication and compression. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data have been presented for three full scaled batches of both product strengths in accordance with relevant European guidelines.

Control of excipients

The excipients comply with Ph.Eur. requirements, including control of relevant functionality-related characteristics. These specifications are acceptable.

Quality control of drug products

The finished product specifications are adequate to control the relevant parameters for the dosage forms. The specification includes tests for description, identification, water content, uniformity of dosage units, dissolution, related substances, assay, microbiological quality and NDMA. The release and shelf-life requirements are identical, except for water content. 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 from three full scaled batches from the proposed production site have been provided for both strengths, demonstrating compliance with the specification.

Stability of drug products

Stability data on the products have been provided on three production scale batches per strength, which were stored at 25°C/60% RH (18 months) and 40°C/75% RH (six months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/PVdC-Al blisters. The stability data show no clear trends or changes in any of the tested parameters at both storage conditions and all parameters remained well within the specified limits. Photostability studies were performed in accordance with ICH recommendations and showed that the products are stable when exposed to light. The claimed shelf-life of 24 months is justified. The labelled storage conditions are: "This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from moisture."

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the products nor have any been used in the manufacturing of these products, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Metformin hydrochloride ELC have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished products.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Metformin hydrochloride ELC is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

The products are generic formulations of Glucophage XR, 500 mg and 750 mg prolonged-release tablets, which are available on the European market. Reference is made to preclinical data obtained with these innovator products. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Metformin hydrochloride is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted two bioequivalence studies per product strength, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted bioequivalence studies in which the pharmacokinetic profiles of the test products Metformin hydrochloride ELC 500 mg and 750 mg prolonged-release tablets (ELC GROUP s.r.o., Chez Republic) are compared with the pharmacokinetic profiles of the reference products Glucophage SR 500 mg and 750 mg prolonged-release tablets (Merck Serono Ltd, United Kingdom). The choice of the reference products from the UK is considered acceptable. Bioequivalence studies were conducted on both strengths because there is a slight variation in composition between strengths.

The bioequivalence studies performed for both strengths were a single-dose fasting study and a single-dose study under fed conditions. Since Metformin hydrochloride ELC are prolonged-release tablets, submission of studies under both fasting and fed conditions was considered adequate. According to the guideline on the pharmacokinetic and clinical evaluation of modified release dosage (EMA/CHMP/EWP/280/96 Rev1), “a multiple-dose study is needed unless a single dose study has been performed with the highest strength which has demonstrated that the mean $AUC_{(0-\tau)}$ after the first dose covers more than 90% of mean $AUC_{(0-\infty)}$ for both test and reference, and consequently a low extent of accumulation is expected. In this case bioequivalence needs to be demonstrated for additional parameters representing the shape of the plasma concentration versus time curve in the single dose study. An early partial $AUC_{(0\ -\ \text{cut-off t})}$ and a terminal partial $AUC_{(\text{cut-off t}\ -\ \text{t last})}$, separated by a predefined cut-off time point, e.g. the half of the dosage interval are recommended, unless otherwise scientifically justified.” Therefore, the MAH provided additional data on pharmacokinetic parameters.

The choice of the reference product in the bioequivalence study has been justified by a comparison of dissolution results and compositions between drug products and reference products. The formulas and preparation of the bioequivalence batches are identical to the formulas proposed for marketing.

Bioequivalence studies

Study designs

- Study I: 500 mg of metformin hydrochloride, fasting conditions.

A single-dose, randomised, open label, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 40 healthy subjects, aged 20-41 years. Each subject received a single dose (500 mg) of one of the two metformin hydrochloride formulations. The tablet was orally administered with 240 ml of 20% glucose solution in water after an overnight fast of at least ten hours. There were two dosing periods, separated by a washout period of ten days. Blood samples were collected pre-dose and at 1, 2, 3, 4, 4,5 5, 5.5 6, 6.5, 7, 7,5 8, 9, 10, 12, 16, 20, 24, 30 and 36 hours after administration of the products.

- Study II: 500 mg of metformin hydrochloride, fed conditions.

A single-dose, randomised, open label, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 40 healthy subjects, aged 20-37 years. Each subject received a single dose (500 mg) of one of the two metformin hydrochloride formulations. The tablet was orally administered with 240 ml of 20% glucose solution in water after an overnight fast of at least ten hours, and 30 minutes after the start of a high caloric, high fat breakfast (energy content: 941 kcal; 59 g fat). There were two dosing periods, separated by a washout period of seven days. Blood samples were collected pre-dose and at 1, 2, 3, 4, 4,5 5, 5.5 6, 6.5, 7, 7,5 8, 9, 10, 12, 16, 20, 24, 30 and 36 hours after administration of the products.

- Study III: 750 mg of metformin hydrochloride, fasting conditions.

A single-dose, randomised, open label, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 40 healthy subjects, aged 18-43 years. Each subject received a single dose (750 mg) of one of the two metformin hydrochloride formulations. The tablet was orally administered with 240 ml of 20% glucose solution in water after an overnight fast of at least ten hours. There were two dosing periods, separated by a washout period of ten days. Blood samples were collected pre-dose and at 1, 2, 3, 4, 4,5 5, 5.5 6, 6.5, 7, 7,5 8, 9, 10, 12, 16, 20, 24, 30 and 36 hours after administration of the products.

- Study IV: 750 mg of metformin hydrochloride, fed conditions.

A single-dose, randomised, open label, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 40 healthy subjects, aged 19-43 years. Each subject received a single dose (750 mg) of one of the two metformin hydrochloride formulations. The tablet was orally administered with 240 ml of 20% glucose solution in water after an overnight fast of at least ten hours, and 30 minutes after the start of a high caloric, high fat breakfast (energy content: 941 kcal; 59 g fat). There were two dosing periods, separated by a washout period of seven days. Blood samples were collected pre-dose and at 1, 2, 3, 4, 4,5 5, 5.5 6, 6.5, 7, 7,5 8, 9, 10, 12, 16, 20, 24, 30 and 36 hours after administration of the products.

The designs of the studies are acceptable. Metformin is advised to be taken with food. A glucose solution was given during administration of the tablet and during the study period, which is acceptable.

Analytical/statistical methods
The analytical methods have been adequately validated and are considered acceptable for analysis of the plasma samples. The methods used in the studies for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

- Study I: 500 mg of active substance; fasting conditions.

One subject was withdrawn from the study since the subject did not turn-up in period II. 39 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of metformin hydrochloride 500 mg under fasted conditions.

Treatment N=39	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	6329 ± 1942	6518 ± 1964	684 ± 173	5.5 (2.0 - 10.0)
Reference	6186 ± 2025	6391 ± 2053	650 ± 181	5.5 (3.0 - 12.0)
***Ratio (90% CI)**	1.038 (0.95 - 1.13)	1.034 (0.95 – 1.12)	1.065 (0.96 – 1.18)	--
CV (%)	22.6	22.1	26.9	--

$AUC_{0-\infty}$ 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
CV coefficient of variation

**ln-transformed values*

- Study II: 500 mg of active substance, fed conditions.

Six subjects were withdrawn from the study due to noncompliance to the high fat, high caloric breakfast (one subject), adverse event (vomiting; four subjects) and not turning-up for period II (one subject). 34 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of metformin hydrochloride 500 mg under fed conditions.

Treatment N=34	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	6767 ± 1715	7057 ± 1742	613 ± 139	7.5 (3.0-10.0)
Reference	6727 ± 1666	6985 ± 1645	591 ± 158	7.5 (4.0-12.0)
***Ratio (90% CI)**	0.998 (0.93-1.07)	1.001 (0.93-1.07)	1.043 (0.99-1.09)	--
CV (%)	17.5	17.4	11.7	--

$AUC_{0-\infty}$ 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
CV coefficient of variation

**ln-transformed values*

- Study III: 750 mg of metformin hydrochloride, fasting conditions.

All 40 subjects were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of metformin hydrochloride 750 mg under fasted conditions.

Treatment N=40	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	8552 ± 2558	8754 ± 2570	964 ± 242	5.0 (2.0 - 12.0)
Reference	9105 ± 3600	9409 ± 3689	956 ± 293	5.0 (2.0 - 10.0)
***Ratio (90% CI)**	0.977 (0.89-1.07)	0.968 (0.88-1.06)	1.030 (0.96-1.10)	--
CV (%)	25.5	25.3	17.9	--

$AUC_{0-\infty}$ 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
CV coefficient of variation

**ln-transformed values*

- Study IV: 750 mg of metformin hydrochloride, fed conditions.

Seven subjects were withdrawn from the study due to adverse events (vomiting). 33 subjects were eligible for pharmacokinetic analysis.

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of metformin hydrochloride 750 mg under fed conditions.

Treatment N=33	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	10752 ± 2689	11051 ± 2702	939 ± 224	8.0 (4.5 - 10.0)
Reference	10968 ± 2874	11268 ± 2876	876 ± 196	7.5 (4.5 - 12.0)
***Ratio (90% CI)**	0.980 (0.94 - 1.02)	0.980 (0.94 - 1.02)	1.070 (1.02 – 1.12)	--
CV (%)	9.9	9.7	11.9	--

$AUC_{0-\infty}$ 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
CV coefficient of variation

**ln-transformed values*

To support the bioequivalence, the MAH provided additional pharmacokinetic data derived from the single-dose studies. The percentage of accumulation was calculated for both product strengths, which showed that the accumulation is low (less than 10%). The 90% confidence intervals for partial AUCs on the T_{max} of Metformin hydrochloride ELC 500 mg in the fed study were calculated, as well as the ratio's to the partial AUCs of the reference product (T/R ratio) (Table 5). The actual median T_{max} (7.50 hour) was considered as cut-off time point, which was sufficiently supported.

Table 5. Partial AUC on T_{max} of metformin hydrochloride 500 mg under fed conditions

Partial $AUC_{0-7.50h}$			**Partial $AUC_{7.50-12h}$**			**Partial $AUC_{7.50-24h}$**		
90% CI Lower	90% CI Upper	T/R ratio (%)	90% CI Lower	90% CI Upper	T/R ratio (%)	90% CI Lower	90% CI Upper	T/R ratio (%)
96.85	113.65	104.92	91.34	110.33	100.39	86.56	109.71	97.45

Furthermore, the MAH provided additional data on pharmacokinetic parameters for the 750 mg product strength, representing the shape of the plasma concentration versus time curve in the single dose studies. Here, the AUC_{0-24} was considered as τ-value, which is based on the daily dosing interval. The 90% confidence intervals for the partial AUCs (AUC_{0-12} and AUC_{12-36}) and the ratio's to the partial AUCs of the reference product are shown in Table 6.

Table 6. Partial AUCs of metformin hydrochloride 750 mg

Partial AUC_{0-12h}			**Partial AUC_{12-36h}**		
90% CI Lower	90% CI Upper	T/R ratio (%)	90% CI Lower	90% CI Upper	T/R ratio (%)
99.31	108.79	103.94	80.95	93.32	86.91

Conclusion on bioequivalence studies

In all four single-dose studies, the 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. The additional data supported that for both prolonged-release product strengths, a multiple-dose study was not considered necessary. For the 500 mg strength, the partial AUC_{0-12}, $AUC_{0-7.5}$, and $AUC_{7.5-12}$, and $AUC_{7.5-24}$ were all within the limits for acceptation. Also the other prerequisites for not conducting a multiple-dose study hold true, as the $AUC_{(0-\tau)}$ after the first dose covers more than 90% of mean $AUC_{(0-\infty)}$. Regarding the 750 mg tablets, bioequivalence between the test and reference product was demonstrated for partial AUC_{0-12h} and AUC_{12-36h}. Here, the other prerequisites for not conducting a multiple-dose study hold true as well. Therefore, it was agreed that for both strengths a multiple-dose study is not warranted.

Based on the submitted bioequivalence studies and the additional data, Metformin hydrochloride ELC 500 mg and 750 mg prolonged-release tablets are considered bioequivalent with Glucophage SR 500 mg and 750 mg prolonged-release tablets.

The MEB has been assured that the bioequivalence studies have 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).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Metformin hydrochloride ELC.

Table 7. Summary table of safety concerns as approved in RMP

Important identified risks	Lactic acidosis
Important potential risks	Leucocytoclastic vasculitis
Missing information	Use during pregnancy and lactation

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the European reference products Glucophage XR. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies that the pharmacokinetic profiles of the products are similar to the pharmacokinetic profiles of the UK reference products. Risk management is adequately addressed. These generic medicinal products can be used instead of the European reference products.

V. USER CONSULTATION

The package leaflet (PL) 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 four participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

The results show that the PL 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

Metformin hydrochloride ELC 500 mg and 750 mg prolonged-release tablets have a proven chemical-pharmaceutical quality and are generic forms of Glucophage XR, 500 mg and 750 mg prolonged-release tablets. Glucophage XR are well-known medicinal products with an established favourable efficacy and safety profile.

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

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 Metformin hydrochloride ELC with the reference products, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 17 March 2021.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse