COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Dipyridamol/Acetylsalicylzuur Sandoz 200/25 mg, modified-release capsules, hard (dipyridamole/acetylsalicylic acid)

NL/H/4440/001/DC

Date: 20 February 2023

This module reflects the scientific discussion for the approval of Dipyridamol/Acetylsalicylzuur Sandoz 200/25 mg, modified-release capsules, hard. The procedure was finalised in the United Kingdom (UK/H/5033/001/DC). After a transfer in 2018, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.

Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

SVELUX 200MG/25MG MODIFIED-RELEASE CAPSULES, HARD

Procedure No: UK/H/5033/001/DC

UK Licence No: PL 04416/1362

Sandoz Limited

LAY SUMMARY

On 16 August 2012, Belgium, Germany, the Netherlands and the UK agreed to grant a Marketing Authorisation to Orion Corporation for the medicinal product Svelux 200mg/25mg modified-release capsules, hard (PL 00289/1664; UK/H/5033/001/DC). The licence was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After the national phase, a Marketing Authorisation was granted in the UK on 9 October 2012.

Svelux 200mg/25mg modified-release capsules contain two different medicines, dipyridamole and aspirin (acetylsalicylic acid). Both belong to a group of medicines called 'anti-thrombotic medicines'. Aspirin also belongs to a group of medicines called 'non-steroidal anti-inflammatory drugs (NSAIDs)'.

Svelux 200mg/25mg modified-release capsules belong to a group of medicines called 'anti-thrombotic agents'. They are used to stop blood clots forming. This medicine is used in people who have had a stroke or transient ischaemic attack (TIA) which are caused by a clot on the brain. This medicine reduces the risk of this happening again.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Svelux 200mg/25mg modified-release capsules, hard outweigh the risks; hence, a Marketing Authorisation was granted.

On 18 October 2012, a change of ownership was granted to change the marketing authorisation holder to Sandoz Limited (PL 04416/1362).

TABLE OF CONTENTS

Module 1

Product Name	Svelux 200mg/25mg modified-release capsules, hard
Type of Application	Generic, Article 10(1)
Active Substances	Acetylsalicylic acid and dipyridamole
Form	Modified-release capsule, hard
Strength	200mg dipyridamole and 25mg acetylsalicylic acid
MA Holder	Sandoz Limited, Frimley Business Park, Frimley, Camberley, Surrey, GU16 7SR, UK
Reference Member State (RMS)	UK
Concerned Member States (CMS)	Belgium, Germany, the Netherlands
Procedure Number	UK/H/5033/001/DC
Timetable	Day 210 – 16 August 2012

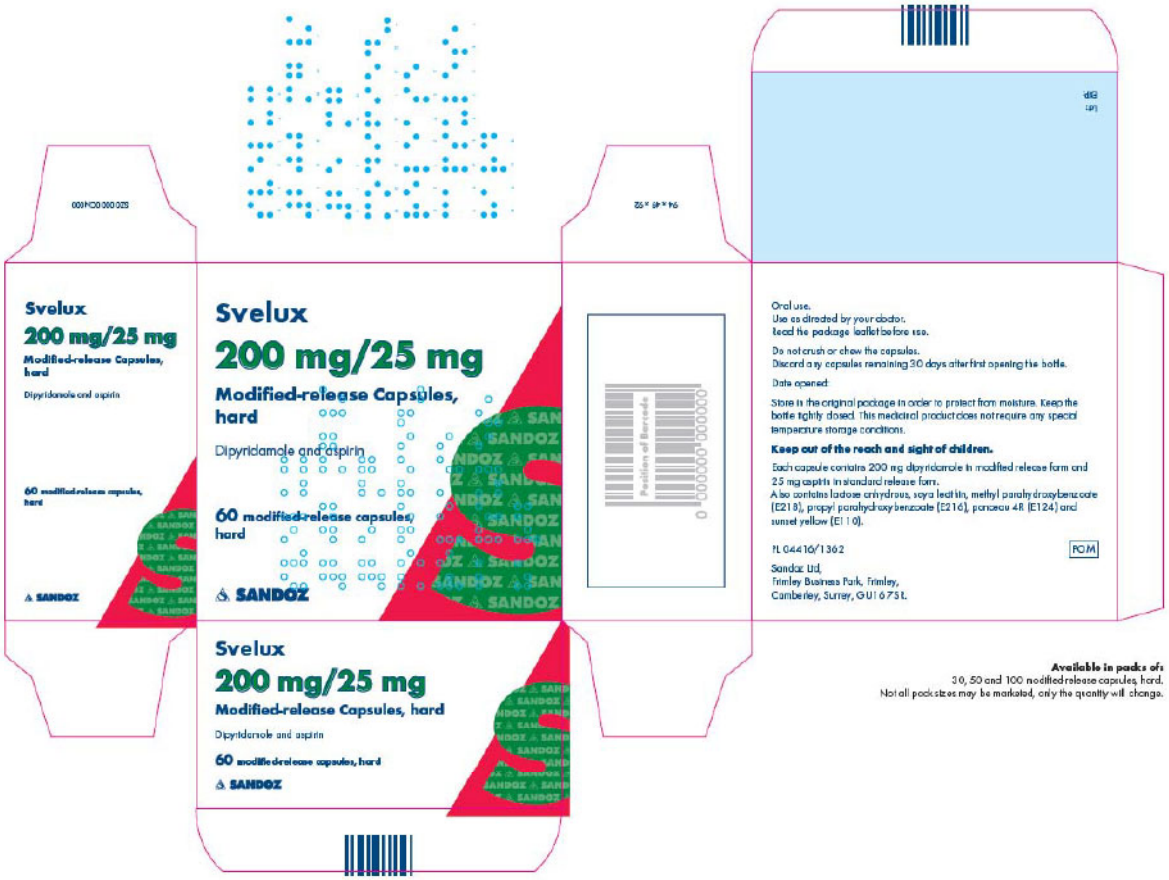
Module 2
Summary of Product Characteristics

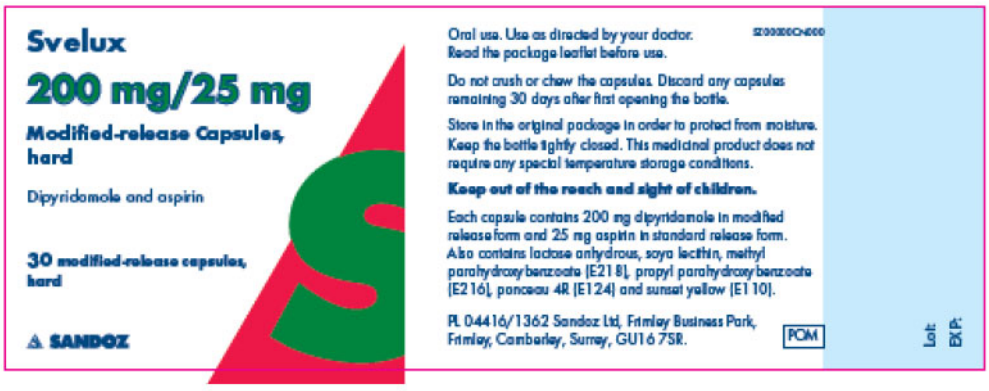
The current approved UK version of the Summary of Product Characteristics (SmPC) for this product is available on the MHRA website.

Module 3
Patient Information Leaflet

The current approved UK version of the Patient Information Leaflet (PIL) for this product is available on the MHRA website.

Module 4
Labelling





Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Svelux 200mg/25mg modified-release capsules, hard (PL 00289/1664; UK/H/5033/001/DC) could be approved. This application was submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS), and Belgium, Germany and the Netherlands as Concerned Member States (CMS).

These are prescription-only medicines indicated for the secondary prevention of ischaemic stroke and transient ischaemic attacks.

This was an application made under the Decentralised Procedure (DCP), according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of the originator product Asasantin Retard 200mg/25mg modified-release capsules, hard (Boehringer Ingelheim Limited), which was initially granted in the UK in May 1998.

Dipyridamole and acetylsalicylic acid (aspirin) are antiplatelet agents. It has been suggested that dipyridamole acts by increasing platelet cyclic 3′,5′-adenosine monophosphate (cAMP) concentrations through the inhibition of adenosine uptake into platelets, affecting platelet aggregation caused by collagen, platelet-activating factor and ADP. Dipyridamole also inhibits platelet cyclic-3′,5′- guanosine monophosphate (cGMP) phosphodiesterase, which in turn inhibits platelet activation and aggregation. Additionally, dipyridamole stimulates prostacyclin synthesis and potentiates the antiplatelet effects of prostacyclin. These actions are generally reversible. Acetylsalicylic acid inactivates irreversibly the enzyme cyclo-oxygenase in platelets thus preventing the production of thromboxane A2, a powerful inducer of platelet aggregation and vasoconstriction. Whereas aspirin inhibits only platelet aggregation, dipyridamole in addition inhibits platelet activation and adhesion. Therefore, an additional benefit from combining both drugs can be expected.

The combination of extended-release dipyridamole 200mg with immediate-release acetylsalicylic acid 25mg was studied in a large randomized trial in patients with recent history of ischaemic stroke or transient ischemic attack (TIA). The combination showed significantly greater efficacy at reducing the risk of stroke compared to placebo but also compared to aspirin or dipyridamole monotherapies. Based on those findings, among others, extended-release dipyridamole with acetylsalicylic acid is currently licensed for the secondary prevention of ischaemic stroke and transient ischaemic attacks.

No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

Three bioequivalence studies were submitted, comparing the pharmacokinetics of the test product Svelux 200mg/25mg modified-release capsules, hard versus the German reference product Aggrenox 200mg/25mg Retard Capsules (Boehringer Ingelheim Pharma GmbH and Co KG) under (i) fasted conditions, (ii) fed conditions and (iii) steady state fasted conditions.

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for these product types at all sites responsible for the manufacture, assembly and batch release of this product.

The RMS and CMS considered that the application could be approved with the end of procedure (Day 210) on 16 August 2012. After a subsequent national phase, the licence was granted in the UK on 9 October 2012.

On 18 October 2012, a change of ownership was granted to change the marketing authorisation holder to Sandoz Limited (PL 04416/1362).

II. ABOUT THE PRODUCT

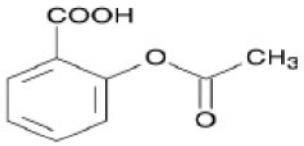
Name of the product in the Reference Member State	Svelux 200mg/25mg modified-release capsules, hard
Name(s) of the active substance(s) (INN)	Acetylsalicylic acid and dipyridamole
Pharmacotherapeutic classification (ATC code)	Platelet aggregation inhibitors, excluding heparin (B01 AC)
Pharmaceutical form and strength(s)	200mg dipyridamole and 25mg acetylsalicylic acid, modified-release capsule, hard
Reference numbers for the Mutual Recognition Procedure	UK/H/5033/001/DC
Reference Member State	United Kingdom
Member States concerned	Belgium, Germany, the Netherlands
Marketing Authorisation Number(s)	PL 04416/1362
Name and address of the authorisation holder	Sandoz Limited, Frimley Business Park, Frimley, Camberley, Surrey, GU16 7SR, UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance – Acetylsalicylic acid

rINN: Acetylsalicylic acid
Chemical name: 2-(acetyloxy)benzoic acid, 2-acetoxybenzoic acid
Structure:



Molecular formula: $C_9H_8O_4$
Molecular weight: 180.2
Appearance: A white crystalline powder or colourless crystals.
Solubility: Slightly soluble in water, freely soluble in ethanol (96%) and soluble in ether

Acetylsalicylic acid is the subject of a European Pharmacopoeia monograph.

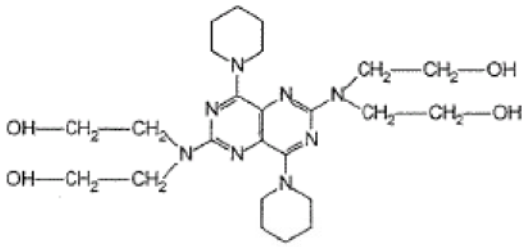
All aspects of the manufacture and control of acetylsalicylic acid are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

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

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

S. Active substance – Dipyridamole

rINN: Dipyridamole
Chemical name: 2,2',2",2"'-[[4,8-di(piperidin-1-yl)pyrimido[5,4-d]pyrimidine-2,6-diyl)dinitrilo]tetraethanol, ethanol,2,2',2",2"'-"-[[4,8-di(piperidin-1-yl)pyrimidol[5,4-d] pyrimidine-2,6-diyl)dinitrilo]tetrakis
Structure:



Molecular formula: $C_{24}H_{40}N_8O_4$
Molecular weight: 504.6
Appearance: A bright yellow crystalline powder
Solubility: Practically insoluble in water and in ether, freely soluble in acetone and soluble in ethanol.

Dipyridamole is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of acetylsalicylic acid are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

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

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients, namely tartaric acid, hypromellose, acacia, talc, povidone, methacrylic acid-methyl methacrylate copolymer (1:2), hypromellose phthalate, dimethicone 350, triacetin, stearic acid, microcrystalline cellulose, lactose anhydrous, pre-gelatinised corn starch, colloidal anhydrous silica, stearic acid, polyvinyl alcohol – part hydrolysed, titanium dioxide (E171), quinoline yellow aluminium lake (E104), soya lecithin (E322), xanthan gum (E415), gelatin, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), ponceau 4R (E124), patent blue V (E131), sunset yellow (E110), shellac, black iron oxide (E172) and potassium hydroxide.

All excipients comply with their respective European Pharmacopoeia monograph, with the exception of quinoline yellow (E104), ponceau 4R (E124), patent blue V (E131), sunset yellow (E110) and soya lecithin, which comply with a suitable in-house specifications and European guidelines concerning the use of colorants. Suitable batch analysis data have been provided for all excipients, showing compliance with their respective specifications.

With the exception of gelatin, none of the excipients are sourced from animal or human origin. The suppliers of gelatin have provided European Directorate for the Quality of Medicines (EDQM) Certificates of Suitability to show that the gelatin is sourced in-line with current requirements for the minimisation of transmission of BSE/TSE. No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development

The objective of the development programme was to formulate a globally acceptable, stable and bioequivalent product that could be considered a generic medicinal product of the originator product Asasantin Retard 200mg/25mg modified-release capsules, hard (Boehringer Ingelheim Limited).

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution profiles and physico-chemical characteristics have been provided for the proposed product versus the originator product.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the finished product. The manufacturing process has been validated using full-scale batches and has shown satisfactory results.

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the

release specifications. Certificates of analysis have been provided for all working standards used.

Container-Closure System
The finished product is packaged in white high-density polyethylene bottles with child-resistant closures, which are packed into cartons in pack sizes of 30, 50 60 and 100 capsules.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years, with instructions to "Discard any capsules remaining 30 days after first opening the bottle" and storage conditions of "Store in the original package in order to protect from moisture. Keep the bottle tightly closed."

Bioequivalence/bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ('user testing'), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Marketing Authorisation Application (MAA) form
The MAA form is pharmaceutically satisfactory.

Quality Overall Summary (Expert report)
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.

III.2 NON-CLINICAL ASPECTS

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

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product's pharmacology and toxicology.

Suitable justification has been provided for the non-submission of an environmental risk assessment. As this product is intended for generic substitution with products that are currently marketed, no increase in environmental burden is expected.

There are no objections to the approval of this product from a non-clinical viewpoint.

III.3 CLINICAL ASPECTS

Pharmacokinetics

In support of this application, the Marketing Authorisation Holder has submitted the following three bioequivalence studies:

Study 1:

An open-label, randomised, two-period, two-treatment, two-sequence, single-dose, crossover study to compare the pharmacokinetics of the test product Orisantin 200mg/25mg modified-release capsules (Orion Corporation) versus the reference product Aggrenox 200mg/25mg Retard Capsules (Boehringer Ingelheim Pharma GmbH & Co KG) in healthy adult subjects under fasted conditions.

Volunteers were dosed with either treatment after an overnight fast of at least 10 hours. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 48 hours post dose. The two treatment arms were separated by a 15-day washout period.

The pharmacokinetic results (presented as geometric least-squares means, ratios and 90% confidence intervals) are presented below:

Parameters (Units)	In-transformed Data			90% Confidence Interval
	Geometric Least Squares Mean			
	Test Product-B	Reference Product-A	Ratio (B/A)	
Dipyridamole:				
C_{max} (ng/mL)	2134.316	2108.078	101.24	95.50-107.34
AUC_{0-t} (ng.h/mL)	13087.228	13729.333	95.32	89.71-101.29
$AUC_{0-\infty}$ (ng.h/mL)	13299.062	13690.099	97.14	91.76-102.85
Salicylic acid:				
C_{max} (ng/mL)	2073.19	2118.34	97.87	93.26-102.71
AUC_{0-t} (ng.h/mL)	6584.68	6696.13	98.34	96.32-100.39
$AUC_{0-\infty}$ (ng.h/mL)	6974.27	7186.74	97.04	94.66-99.49
Acetylsalicylic acid:				
C_{max} (ng/mL)	410.76	407.28	100.85	94.32-107.84
AUC_{0-t} (ng.h/mL)	369.73	358.85	103.03	98.72-107.53
$AUC_{0-\infty}$ (ng.h/mL)	374.35	362.58	103.25	98.91-107.77

The 90% confidence intervals for all actives lie within the acceptance criteria specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), meaning that bioequivalence has been shown between the test and reference products.

Study 2:
An open-label, randomised, two-period, two-treatment, two-sequence, single-dose, crossover study to compare the pharmacokinetics of the test product Orisantin 200mg/25mg modified-release capsules (Orion Corporation) versus the reference product Aggrenox 200mg/25mg Retard Capsules (Boehringer Ingelheim Pharma GmbH & Co KG) in healthy adult subjects under fed conditions.

Volunteers were dosed with either treatment after an overnight fast of at least 11 hours and a high-fat, high-calorie breakfast. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 48 hours post dose. The two treatment arms were separated by a 14-day washout period.

The pharmacokinetic results (presented as geometric least-squares means, ratios and 90% confidence intervals) are presented below:

Parameters (Units)	In-transformed Data			90% Confidence Interval
	Geometric Least Squares Mean			
	Test Product-B	Reference Product-A	Ratio (B/A)	
Dipyridamole:				
C_{max} (ng/mL)	1779.724	1600.764	111.18	102.36-120.76
AUC_{0-t} (ng.h/mL)	13661.694	13134.905	104.01	95.38-113.43
$AUC_{0-\infty}$ (ng.h/mL)	13907.694	13342.980	104.23	95.39-113.88
Salicylic acid:				
C_{max} (ng/mL)	1083.16	1075.80	100.68	95.97-105.63
AUC_{0-t} (ng.h/mL)	4441.01	4389.81	101.17	98.11-104.31
$AUC_{0-\infty}$ (ng.h/mL)	4820.20	4720.13	102.12	98.86-105.49
Acetylsalicylic acid:				
C_{max} (ng/mL)	137.120	125.098	109.61	99.97-120.19
AUC_{0-t} (ng.h/mL)	199.339	188.757	105.61	100.70-110.75
$AUC_{0-\infty}$ (ng.h/mL)	213.736	198.922	107.45	103.11-111.97

The 90% confidence intervals for all actives lie within the acceptance criteria specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), meaning that bioequivalence has been shown between the test and reference products.

Study 3:
An open-label, randomised, two-period, two-treatment, two-sequence, multiple-dose, crossover study to compare the rate/extent of absorption of the test product Orisantin 200mg/25mg modified-release capsules (Orion Corporation) versus the reference product Aggrenox 200mg/25mg Retard Capsules (Boehringer Ingelheim Pharma GmbH & Co KG) in healthy adult subjects under fasting conditions.

Volunteers were dosed for four consecutive days with either treatment every 12 hours, then received one dose in the morning of the fifth day. Blood samples were taken for the measurement of pharmacokinetic parameters pre- and up to 12 hours post the morning dose. The two treatment arms were separated by an 8-day washout period.

The pharmacokinetic results (presented as arithmetic means, ratios and 90% confidence intervals) are presented below:

Parameters (Units)	Arithmetic Means			90% Confidence Interval
	Test Product-B	Reference Product-A	Ratio (B/A)	
Dipyridamole:				
$C_{max,ss}$ (ng/mL)	2045.764	2109.301	97.427	92.691-102.404
AUC_{ss} (ng.h/mL)	13638.091	14222.754	96.956	91.833-102.364
$C_{min,ss}$ (ng/mL)	644.354	680.800	98.123	91.296-105.461
Salicylic acid:				
$C_{max,ss}$ (ng/mL)	1210.842	1236.780	97.823	95.054-100.672
AUC_{ss} (ng.h/mL)	3313.233	3315.577	99.933	98.280-101.613
%ptf*	449.132	458.146	97.835	95.133-100.614
Acetylsalicylic acid:				
$C_{max,ss}$ (ng/mL)	359.480	389.830	93.408	86.491-100.879
AUC_{ss} (ng.h/mL)	303.971	298.583	101.674	96.482-107.146

* peak trough fluctuation was calculated instead of $C_{min,ss}$ as all $C_{min,ss}$ values equal to 0 except for two patients.

The 90% confidence intervals for all actives lie within the acceptance criteria specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98). Therefore, bioequivalence has been shown between the test and reference products.

Efficacy

No new data on the efficacy have been submitted and none are required for this type of application.

Safety

With the exception of the data submitted during the bioequivalence study, no new safety data were submitted and none were required. No new or unexpected safety issues were raised by the bioequivalence data.

SmPC, PIL and Labels

The SmPC, PIL and labels are medically acceptable. The SmPC is consistent with that for the originator product.

Pharmacovigilance System and Risk Management Plan

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a risk management plan for this product.

Clinical Expert Report

The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Conclusion

The grant of a Marketing Authorisation is recommended.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Svelux 200mg/25mg modified-release capsules, hard are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for an application of this type.

CLINICAL

Bioequivalence has been demonstrated between the applicant's product and the reference product Aggrenox 200mg/25mg Retard Capsules (Boehringer Ingelheim Pharma GmbH and Co KG).

No new or unexpected safety concerns arose from this application.

The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product.

BENEFIT-RISK ASSESSMENT

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's product and the originator product are interchangeable. Extensive clinical experience with acetylsalicylic acid and dipyridamole is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is therefore considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome