LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Hypolivat,
(acetylsalicylic acid, rivaroxaban)

SE/H/2760/001/DC

This module reflects the scientific discussion for the approval of Hypolivat. The procedure was finalised at 2025-11-17. For information on changes after this date please refer to the module 'Steps taken after the finalisation of the initial procedure - Summary'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Hypolivat, 2,5 mg/50 mg, Capsule, hard.

The active substance is acetylsalicylic acid, rivaroxaban. A comprehensive description of the indication and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1 Rationale for the product

The application concerns Rivaroxaban/Acetylsalicylic acid 2.5 mg/50 mg hard capsules, a fixed dose combination (FDC), in accordance with Article 10b of the Directive 2001/83/EC. The new FDC product, Rivaroxaban/Acetylsalicylic acid 2.5 mg/50 mg hard capsules, is intended to be used both as initial treatment and as substitution treatment, and the proposed indication is in line with the currently approved co-administration of low-dose rivaroxaban and acetylsalicylic acid (ASA), either alone, or with clopidogrel or ticlopidine, for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers and for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events.

A 50 mg immediate-release (IR) Aspirin tablet is currently not available to make a head-to-head comparison with the 50 mg ASA dose contained in the FDC, therefore, the reference treatment consisted of Xarelto 2.5 mg film-coated tablet BID coadministered with Aspirin N (ASA) 100 mg tablet QD. As per the "Position paper on the regulatory requirements for the authorisation of low-dose modified release ASA formulations in the secondary prevention of cardiovascular events" (*Position paper EMA 2002*), the reduction of TxB_2 levels in serum (not in plasma) can be considered as an accepted surrogate for platelet aggregation and also for efficacy in secondary prevention of CV events. According to this position paper, solid and robust evidence indicating equivalence / non-inferiority regarding TxB_2 levels should be presented, when a modified release (MR) ASA formulation needs to be compared wth IR ASA formulation. Pharmacodynamic equivalence based on TxB_2 kinetics (t_{max}, maximal % of inhibition and AUC as well) should be assessed after single as well as repeated doses in a sufficient population of both healthy volunteers (at least approx. 40) and patients (number to be determined and justified by the applicant) to allow the detection of possible resistances or non-responders. The proposed FDC developed by the applicant, is an IR formulation, however EMA's scientific advice was based on these regulatory requirements, therefore the conducted PK/PD trial was based on this position paper.

II.2 About the product

Rivaroxaban, an oral, highly selective direct activated factor X (Xa) inhibitor, is an anticoagulant. Rivaroxaban inhibits both free and prothrombinase-bound factor Xa. Unlike heparin, and the low molecular weight heparins, rivaroxaban binds directly to the active site of factor Xa without the need for a cofactor (e.g., antithrombin III). Rivaroxaban inhibits factor Xa with more than 100,000-fold greater selectivity than other biologically important serine proteases (e.g., thrombin, trypsin, plasmin, factor VIIa, factor IXa, urokinase, activated protein C) *(Xarelto® product information 2023, Pubchem Rivaroxaban 2022).*

Acetylsalicylic acid (ASA) (chemical name: 2-Acetoxybenzoic acid) is an orally administered non-steroidal anti-inflammatory agent. It binds to and acetylates serine residues in cyclooxygenases, resulting in decreased synthesis of prostaglandin, platelet aggregation, and inflammation. This agent exhibits analgesic, antipyretic, and anticoagulant properties.

The application concerns Rivaroxaban/Acetylsalicylic acid 2.5 mg/50 mg hard capsules, a FDC, in accordance with Article 10b of the Directive 2001/83/EC.

II.3 General comments on the submitted dossier

The application for Hypolivat, 2,5 mg/50 mg, Capsule, hard, is a Combination Art. 10b application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and the following as concerned member states (CMS):
SE/H/2760/001/DC: AT, CZ, DE, FR, HR, HU, PL, PT, RO, SK

The active substances are not considered as new active substances.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

Paediatric Regulation
Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision [P/0516/2022] on the granting of a product specific waiver.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

GMP active substances
Regarding the statement on GMP for the active substances statements/declarations are provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

GCP
A statement on the application of appropriate GCP standards in the submitted studies have been provided. No issues regarding GCP have been identified.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

The structure of the drug substance has been adequately proven, and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described, and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

Drug Product
The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III.2 Non-clinical aspects

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of rivaroxaban and acetylsalicylic acid (ASA) are well known. As rivaroxaban and ASA are a widely used, well-known active substance, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Pharmacology
No new pharmacology studies have been submitted for the fixed dose combination product by the Applicant and none are considered required in this application. The Applicant has summarised the literature concerning pharmacology of rivaroxaban and acetylsalicylic acid in sufficient detail.

Pharmacokinetics
No new pharmacokinetic studies have been submitted for the fixed dose combination product by the Applicant and none are considered required in this application. The Applicant has summarised the literature concerning pharmacokinetics of rivaroxaban and acetylsalicylic acid in sufficient detail.

Toxicology
No new nonclinical toxicology studies have been submitted by the applicant for the fixed dose combination product and none are considered required in this application. The toxicology aspects in the nonclinical overview submitted by the applicant consists of literature references and safety has been characterized in sufficient detail. No safety concerns have been detected. Rivaroxaban (Xarelto) have been available for clinical use since 2008 and Acetylsalicylic acid since 2003, and their safety profile is well characterized (see Clinical AR). In addition, as per the currently approved product information of Xarelto, as well as the national and international guidelines, low-dose rivaroxaban must always be given orally with low dose of ASA, as a pharmacokinetic enhancer, in order to increase its efficacy.

The safety of the combination treatment is considered well characterised since combination of Rivaroxaban and Acetylsalicylic acid is established and well characterised in clinical practice. No clinical safety issues have been raised for the current product (see Clinical AR).
Overall, the applicant has summarised the literature concerning toxicology of Rivaroxaban and acetylsalicylic acid in sufficient detail.

Environmental Risk Assessment (ERA)
The Applicant has submitted two separate ERA-documents for rivaroxaban and acetylsalicylic acid according to the current guideline (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.*).

For both active substances - acetylsalicylic acid and rivaroxaban-, the Applicant refers to previously submitted ERAs which were performed by other MAHs, where it was concluded that acetylsalicylic acid and rivaroxaban are not expected to pose a risk to the environment. Letters of access (LoA) have been sought but not provided. The Applicant provided justifications that the scientific conclusions reached in the ERAs for acetylsalicylic acid and rivaroxaban remain applicable and no further studies are required. This is accepted.

III.3 Clinical aspects

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted a single PKPD study comparing the single dose PK of rivaroxaban of the new fixed dose combination (FDC) product (treatment 1) and the individual tablet rivaroxaban concomitantly administered with acetylsalicylic acid (treatment 2) to establish bioequivalence for rivaroxaban. No other PK studies were presented by the Applicant.

Study PAO P8-022
Methods
A single and multiple dose crossover study (Study PAO-P8-022) was conducted to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of the new FDC. More specifically, the aim of this clinical study was to demonstrate PK equivalence of rivaroxaban after a single dose of the new FDC product, hard gelatin capsule and the individual Xarelto® tablet concomitantly administered with Aspirin® under fasting conditions (cohort 1), and PD equivalence of ASA component of the novel FDC product, administered BID versus the reference product, Aspirin N 100 mg administered QD in combination with Xarelto® 2.5 mg, using the surrogate marker TxB 2 concentrations, and inhibition in healthy and obese adult female and male subjects (cohort 2). In cohort I, C_{max} and AUC_{0-t} of rivaroxaban following single dose administration are assessed as primary endpoints for rivaroxaban, while C_{max}/D, T_{max}, AUC_{0-t}/D of ASA following single dose administration are assessed as secondary endpoints for ASA.

Blood samples for concentration analysis were collected pre-dose and up to 36- and 12-hours post-dose for rivaroxaban and ASA, respectively. Plasma concentrations of rivaroxaban and ASA were determined with a Reversed-phase HPLC /MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max} (primary endpoints) for rivaroxaban and descriptive statistics were used to analyse ASA secondary PK endpoints. The PD equivalence of the ASA component of the novel FDC product is described in the Clinical AR.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters for rivaroxaban and ASA

Parameters	Treatment-1 N=23	Treatment-2 N=23	Geometric mean ratio (90% CI)	ISCV (%)
Rivaroxaban				
T_{max} (h)	2.02 (1.00-3.50)	1.50 (0.72-4.00)	N/A	N/A
C_{max} (ng/mL)	82.83 (21.90)	77.76 (26.48)	107.37 (96.90-118.97)	16.8
AUC_{0-T} (ng*h/mL)	470.90 (120.12)	450.04 (93.72)	103.01 (96.08-110.44)	11.4
ASA				
T_{max} (h)	0.67 (0.33-1.55)	0.67 (0.17-2.00)	N/A	N/A
C_{max}/D (ng/mL/mg)	16.45 (4.68)	11.98 (4.66)	141.87 (117.14-171.83)	32.0
AUC_{0-T}/D (ng*h/mL/mg)	14.49 (3.61)	13.18 (3.94)	110.59 (102.19-119.68)	12.9

Abbreviations: ISCV = intra-subject coefficient of variation; N/A = not appliable

Data are presented as mean ± standard deviation (SD) except for T_{max}, for which median (minimum – maximum) is presented

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the rivaroxaban in Treatment 1 (FDC) and Treatment 2 (rivaroxaban and ASA as free combination) fell within the conventional acceptance range of 80.00-125.00%.

Acetylsalicylic acid descriptive statistical analysis showed that dose normalised AUC_{0-t} was comparable between the two treatments, while dose normalised C_{max} was found to be higher in Treatment 1 (FDC) compared to Treatment 2 (rivaroxaban and ASA as free combination).

Discussion and overall conclusion

The PKPD study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). Additionally, the study design was in agreement with scientific advice received from The European Medicines Agency during the development program and the product specific guidance for rivaroxaban (EMA/CHMP/160650/2016). The bioanalytical methods were adequately validated.

According to the Scientific Advice, bioequivalence for rivaroxaban should be evaluated as indicated in the product specific guidance for rivaroxaban (EMA/CHMP/160650/2016). Primary endpoints are AUC_{0-t} and C_{max} with 90% confidence interval of 80-125% as acceptance range. For AUC_{0-t} and C_{max} for rivaroxaban, the 90% confidence interval for the ratio of Treatment-1 and Treatment-2 fell within the conventional acceptance range of 80.00-125.00%.

Although dose normalised C_{max} was found to be higher in Treatment 1 (FDC) compared to Treatment 2 (rivaroxaban and ASA as free combination), the non-dose normalized C_{max} was lower in Treatment 1 compared to Treatment 2, so no safety concerns are expected with the FDC compared to treatment with ASA given as a 100 mg dose. As outlined in the Scientific Advice, interpretability of dose normalized results in terms of showing comparable *in vivo* performance is seen difficult. In addition, such data would not be sufficient in order to confirm if BID dosing of ASA was equally effective as QD dosing and therefore additional PD data would be needed. Dose normalised PK data for ASA are presented as secondary endpoints. Assessment of TE of the ASA component is based on PD data and can be found in the PD section.

Therefore, it can be concluded that the PK profile of rivaroxaban of the new FDC can be considered bioequivalent to the PK profile of Xarelto.

Even though fasting intake of ASA was acceptable for the PK/PD study in healthy subjects, in the Scientific Advice it was stated that whether an administration irrespective of food or, due to potential gastrointestinal adverse events, with food will be recommended in the SmPC is a matter of assessment at the time of a marketing authorisation application, irrespectively of the mode of administration in the PK/PD study. According to Rivaroxaban reference product (Xarelto) SmPC, "Intake with food does not affect rivaroxaban AUC or C_{max} at the 2.5 mg dose". Therefore, it is agreed that Rivaroxaban can be administered irrespective of food intake. The SmPC of the selected ASA reference product, namely Aspirin N 100 mg Tablette, states that medication should not be taken on an empty stomach. However, there are other approved ASA products in the market that can be taken with or without food. Therefore, it is accepted that the proposed product can be taken with or without food.

The Applicant has not presented new PK studies with the proposed fixed dose combination to study distribution, elimination, dose proportionality, intra- and inter-individual variability and pharmacokinetics in target population and refers to already available data for the individual components rivaroxaban and ASA. However, as neither of the mono-components are NCE and the coadministration of rivaroxaban and ASA is established, the absence of dedicated studies is considered acceptable. The proposed SmPC wording is in line with Xarelto and ASA SmPC and is acceptable.

The Applicant has not presented new PK studies with the proposed fixed dose combination in special populations and refers to already available data for the individual component rivaroxaban. According to the Guideline on clinical development of fixed combination medicinal products (EMA/CHMP/58268/2017), "the potential impact of combined pharmacokinetics in vulnerable subgroups (patients with renal impairment, elderly, etc.) should be addressed." However, as neither of the mono-components are NCE and the coadministration of rivaroxaban and ASA is established, the absence of dedicated studies in special populations is considered acceptable. The proposed SmPC wording is in line with Xarelto SmPC and is acceptable.

No interaction study has been performed with the FDC tablet and no specific DDI study to investigate potential interaction between the two compounds has been performed. According to rivaroxaban reference product (Xarelto) SmPC, no clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg acetylsalicylic acid. It is unknown whether rivaroxaban affects ASA PK or PD, however, the combination is already established in clinical practice and the absence of a specific interaction study between rivaroxaban and ASA is therefore acceptable. Interaction studies had been previously performed with the individual components rivaroxaban and ASA and any interaction identified for these individually are also relevant to Hypolivat.

Pharmacodynamics

The applicant presented two studies to demonstrate the equivalence of multiple oral dose administrations of the FDC, administered BID, compared to the coadministration of the currently co-administered treatments for the prevention of atherothrombotic events, Xarelto 2.5 mg film-coated tablets, administered BID, and Aspirin 100 mg tablet, administered once daily (QD), based on the surrogate marker TxB2 concentration. The first study (2764) was a pilot, multiple-dose, randomized, open-label, two-period, two-sequence, two-treatment, single-centre, crossover, concept PD study. The products were studied using a crossover design with 12 subjects (8 healthy adult subjects and 4 adult subjects with obesity [otherwise healthy] non-smoking male and non-pregnant female subjects). The primary PD endpoints of the study were to evaluate the TxB2 concentration (C_{24}) and area under the concentration curve (AUC_{0-24}) after 24 hours following 8 consecutive 100 mg/day doses of ASA from the FDC (50 mg BID) compared to the coadministration of Xarelto and Aspirin (100 mg QD) and the percent inhibition of TxB2 after 24 hours (I_{24}) following 8 consecutive 100 mg/day doses of ASA from the FDC (50 mg BID) compared to the coadministration of Xarelto and Aspirin (100 mg QD).

This study was used to inform the design of the pivotal study PAO-P8-022.

Study PAO-P8-022 was designed to demonstrate PK equivalence of rivaroxaban after a single dose of the new FDC product and the individual Xarelto tablet concomitantly administered with Aspirin under fasting conditions (cohort 1), and PD equivalence of ASA component of the novel FDC product, administered BID versus the reference product, Aspirin N 100 mg administered QD in combination with Xarelto 2.5 mg, using the surrogate marker TxB_2 concentrations, and inhibition in healthy and obese adult female and male subjects (cohort 2). The PD part is summarised below.

Forty-two healthy adult male or female volunteers aged 18 to 55 years, were included in the study. Of these 10 were obese.

A washout was of about 14 days between the last treatment administration on Day 8 of Period 1 and the subsequent treatment administration of Period 2. This period was considered sufficient as the normal mean lifetime and turnover of platelets is 7 to 10 days and for PD parameters to return to baseline levels. This 14-day washout period also allowed for the elimination of rivaroxaban and ASA for more than 10 half-lives and was therefore deemed sufficient to avoid carry-over effect for both drugs

The primary PD objective of the study was to demonstrate equivalence following multiple oral dose administrations between the new FDC product and the individual tablet Aspirin concomitantly administered with Xarelto, based on the surrogate marker TxB_2 levels. The equivalence of the surrogate marker TxB_2 levels was assessed by estimating TxB_2 concentration after 24 hours (C_{24}) and TxB_2 area under the concentration-time curve from time zero to 24 hours (AUC_{0-24}) following 8 consecutive administration days.

The table presents the statistical results for TxB_2 C_{24}

Statistical results for TxB_2 C_{24} following 8 consecutive administration days (Cohort 2)

Treatment	Mean of ln-C24	exp (Mean of ln-C24) [a]	Upper 95% CI
Treatment- 3 (test) (N=38)	0.88	2.41	2.59
Treatment-4 (reference) (N=40)	1.49	4.45	4.77

[a] units are ng/mL for C_{24}

The table below presents the results of comparison on TxB_2 levels, between treatment 3 (test) and treatment 4 (reference), to show PD equivalence of ASA in the 2 treatments.

Comparison of statistical results for TxB_2 following 8 consecutive administration days (Cohort 2)

Parameter	Intra-Subject C.V. (%)	Geometric LSmeans[a]		95% Confidence Intervals (%)		
		Treatment-3 N=38	Treatment-4 N=40	Ratio (%)	Lower	Upper
C_{24}	21.6	2.41	4.45	54.19	49.07	59.86
AUC_{24}	24.6	25.54	41.48	61.56	55.00	68.91

[a] units are ng/mL for C_{24} and ng·h/mL for AUC_{24}

Post-Hoc Analysis to Verify the Achievement of the Target Therapeutic Limit and to Determine the Equivalence Margins.

The equivalence limit estimation was based on the therapeutic range (1 ng/mL to 10 ng/mL of TxB_2). Following the statistical results, an equivalence range based on C_{24} results was estimated to be between 24.05 to 209.68% margins.

The table below presents the determination of the primary post-hoc TxB_2 Equivalence Margins for C_{24}.

TxB_2 Equivalence Margins for C_{24} (Cohort 2)

Parameter	Intra-subject CV (%)	Geometric LSmeans		Ratio (%)	95% CI Equivalence Margins (%)	
		Treatment-3 (N=38)	Treatment-4 (N=40)		Lower	Upper
C_{24} (ng/mL)	21.6	2.41	4.45	54.19	24.05	209.68

The table below presents the determination of the secondary post-hoc TxB_2 Equivalence Margins for AUC_{0-24}.

Secondary TxB_2 Equivalence Margins for AUC_{0-24}. (Cohort 2)

Parameter	Intra-subject CV (%)	Geometric LSmeans		Ratio (%)	95% CI Equivalence Margins (%)	
		Treatment-3 (N=38)	Treatment-4 (N=40)		Lower	Upper
AUC_{24} (h*ng/mL)	24.6	25.54	41.48	61.56	2.61	535.36

The statistical approach and the choice of equivalence margins has been discussed by SAWP/CHMP at different occasions.

As a secondary objective, the inhibition of the surrogate marker TxB_2 estimated over 24 hours (I_{24}) after 8 days oral dose administration and 24 hours (I_{24}) after 1 complete day administration, after 12 hours (I_{12}) after the first dose of ASA, and after 12 hours (I_{12}) following 8 consecutive days administration of ASA was investigted. In addition, TxB_2 levels and AUC_{0-24} after 1 treatment day and TxB_2 levels and AUC_{0-12}, 12 hours after 1 single oral dose administration were calculated.

The table below presents the summary of pharmacodynamic statistical analysis of TxB_2 inhibition parameters after 1 and 8 days of administration of the test and reference products, respectively.

Summary of the Pharmacodynamic Statistical Analysis of TxB_2

Parameter	Intra-subject CV (%)	Geometric LSmeans		Ratio (%)	95% Confidence Limits (%)	
		Treatment- 3 (N=42)	Treatment-4 (N=42)		Lower	Upper
Inhibition Parameters Following 1 Day of Treatment Administration						
I_{12} (%)	9.7	73.30	91.81	79.84	76.50	N/A
I_{24} (%)	3.0	92.97	90.62	102.60	101.26	N/A
Inhibition Parameters Following 8 Days of Treatment Administration						
I_{12} (%)[a]	0.2	99.35	99.48	99.87	99.79	N/A
I_{24} (%)[a]	0.3	99.30	98.65	100.65	100.51	N/A
$E_{max,ss}$ (%)[a]	0.1	99.93	99.94	99.99	99.95	N/A
$AUEC_{0-24}$ (%*h)[b]	0.2	2393.94	2388.36	100.23	100.13	N/A

[a] N=40 for Treatment-3 and Treatment-4

Subjects' responsiveness was also evaluated and categorized. Subjects were categorized as responder (inhibition as successful treatment: I_{24} >97%, responder with incomplete inhibition: I_{24} ≥95% and ≤97%), or non-responder (inhibition as treatment failure: I_{24} <95%). The Table presents the results on subjects' responsiveness.

Summary of Subjects Responsiveness on Day 8 Following Multiple Dose Administration – (Cohort 2)

	Treatment			
	Treatment-3 (N=42)		Treatment-4 (N=42)	
Responsiveness	**n**	**(%)**	**n**	**(%)**
Responder (I_{24} > 97%)	40	100.00	41	97.62
Incomplete Responder (I_{24} ≥ 95% and ≤ 9	0	0.00	1	2.38
Non-Responder (I_{24} < 95%)	0	0.00	0	0.00

III.3.1 Overall conclusion on PK/PD

The PKPD study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing. It can be concluded that the PK profile of rivaroxaban of the new FDC can be considered bioequivalent to the PK profile of Xarelto. The primary PD endpoints of this study shows that the levels of TxB2 after 8 days of treatment administration were lower in the test arm as compared to the control with a ratio well below 1 after 8 days of treatment administration of both C_{24} and AUC_{0-24}. There was a clinically relevant reduction of TxB2 levels corresponding to a virtually complete inhibition in both test arms. Therefore, it can be concluded that the ASA component in the test arm is considered therapeutically equivalent to the reference.

Clinical efficacy
No clinical efficacy studies were conducted for this product. The equivalence of the proposed FDC product administered twice daily and the individual tablet rivaroxaban (twice daily) concomitantly administered with acetylsalicylic acid (once daily), was evaluated in a pivotal PK/PD study (PAO-P8-022) as described above. The applicant has summarized the literature concerning the efficacy of low-dose rivaroxaban treatment for the sought ACD, CAD and PAD indications in sufficient detail.

Clinical safety
The applicant has presented literature summary in sufficient detail and data from studies 2764 and PAO-P8-022 did not reveal unexpected safety findings. Headache and constipation were the most commonly experienced TEAEs in both Test and Reference cohorts. There were no deaths.

Product information

The sought indications are as follows:

<Product name>, alone or with clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers (see sections 4.3, 4.4 and 5.1).

<Product name> is indicated for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events.

It is noted that the proposed FDC product could be interpreted as both initial treatment indication and a substitution treatment indication. This is acceptable as Rivaroxaban/ASA is deemed to fulfil the requirements for both initial and substitution treatment indications according to the Guideline on clinical development of fixed combination medicinal products (EMA/CHMP/158268/2017) considering that rivaroxaban for these indications is to be used concomitantly with ASA at all occasions. Consequently, the sought indications are deemed acceptable.

Pharmacovigilance system
Proposed MAH
SE/H/2760/001/DC: Zentiva, k.s, ZENTIVA FRANCE, Zentiva Pharma GmbH, Zentiva Portugal, Lda
The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System together with an annex listing all relevant subsidiaries. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

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 Hypolivat.

Responding to comments made during assessment the applicant updated Part II-Module SVII by providing an explanation for discrepancies versus the RMPs for the corresponding monocomponent products. In addition, the term “patient alert card” was replaced with “patient card”.

Part II Safety specification

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Haemorrhage
Important potential risks	• Embryo-fetal toxicity
Missing information	• Remedial pro-coagulant therapy for excessive haemorrhage • Patients with atrial fibrillation (AF) and a prosthetic heart valve

Part III Pharmacovigilance Plan

Other routine pharmacovigilance activities beyond adverse reactions reporting and signal detection, include follow-up questionnaires. In line with the originator product RMP for rivaroxaban, the questionnaires for "Liver-related adverse events" and "Renal failure" are added into this RMP. However, these safety concerns are not included in the list of safety concerns as they are not considered important risks in the originator RMP. The follow-up questionnaire forms have been appended in Annex 4 of the RMP. This is endorsed.

Part V Risk minimisation measures

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Haemorrhage	Routine risk minimisation measures:	Routine

	SmPC (sections 4.3, 4.4, 4.5 and 4.8) PIL (section “What you need to know before you take rivaroxaban Do not take rivaroxaban”, “Possible side effects”). • Prescription only medicine. • Limited pack sizes Additional risk minimisation measures: • *Educational material for prescribers (Prescriber guide)* • *Patient cards*	
Safety concern	Risk minimisation measures	Pharmacovigilance activities
Embryo-fetal toxicity	Routine risk minimisation measures: SmPC (section 4.3, 4.6 and 5.3) • Prescription only medicine. • Limited pack sizes Additional risk minimisation measures: *None*	Routine
Remedial pro-coagulant therapy for excessive haemorrhage	Routine risk minimisation measures: SmPC (section 4.9) – Prescription only medicine. – Limited pack sizes Additional risk minimisation measures: *None*	Routine

Patients with atrial fibrillation (AF) and a prosthetic heart valve	Routine risk minimisation measures: SmPC (section 4.4) – Prescription only medicine. – Limited pack sizes Additional risk minimisation measures: *None*	Routine

Part VI Summary of the RMP

The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)

Active substance is currently not listed in the published EURD list
The MAH shall submit the first periodic safety update report for this product containing rivaroxaban acetylsalicylic acid as a combination of active substances in accordance with the rivaroxaban as for the single active substance (with a period of 3 years, with the DLP of 15/09/2027) following authorization. Further, MAHs shall continuously check the European medicines web-portal if the active substance has been included in the list of Union reference dates (EURD list). If yes, after publication in the EURD list the PSURs shall be submitted in accordance with the requirements set out in the EURD list.

Common renewal date
The common renewal date will be 5 years after closure of the DCP.

IV. BENEFIT RISK ASSESSMENT

The quality of the product, Hypolivat, is found adequate and from a quality perspective the application is recommended for approval. There are no objections to approval of Hypolivat, from a non-clinical

and clinical point of view. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

Post approval commitments
N/A

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

Additional risk minimisation measures (including educational material)
The MAH shall provide an educational pack prior to launch, targeting all physicians who are expected to prescribe/use Hypolivat. The educational pack is aimed at increasing awareness about the potential risk of bleeding during treatment with rivaroxaban/acetylsalicylic acid and providing guidance on how to manage that risk. The physician educational pack should contain:
• The Summary of Product Characteristics
• Prescriber Guide
• Patient Cards

The Prescriber Guide should contain the following key safety messages:
• Details of populations potentially at higher risk of bleeding
• Recommendations for dose reduction in at risk populations
• Guidance regarding switching from or to rivaroxaban/acetylsalicylic acid treatment
• Management of overdose situations
• The use of coagulation tests and their interpretation
• That all patients should be counselled about:
  ➢ Signs or symptoms of bleeding and when to seek attention from a health care provider.
  ➢ Importance of treatment compliance
  ➢ Necessity to carry the Patient Card that is included in each pack, with them at all times
  ➢ The need to inform Health Care Professionals that they are taking rivaroxaban/acetylsalicylic acid if they need to have any surgery or invasive procedure.

- **Obligation to conduct post-authorisation measures in accordance with Article 21a of Directive 2001/83/EC**
  N/A

- **Specific obligation to complete post-authorisation measures for the marketing authorisation under Exceptional circumstances in accordance with Article 22 of Directive 2001/83/EC**
  N/A

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available in the MRI Product Index.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available in the MRI Product Index.

V.4.2 Assessment of User Testing

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 language used for the purpose of user testing the PL was English. The user test was assessed and accepted at day 70.

For Hypolivat, a user consultation with target patient groups on the package information leaflet (PL) has been performed regarding layout The bridging regarding layout was assessed and accepted.

VI. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-