LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Acetylsalicylic acid Bluefish (acetylsalicylic acid)

SE/H/2491/01-02/DC

This module reflects the scientific discussion for the approval of Acetylsalicylic acid Bluefish. The procedure was finalised at 2025-08-14. For information on changes after this date please refer to the module 'Update'.

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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 Acetylsalicylic acid Bluefish, 75 mg, 160 mg, Tablet.

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

II. EXECUTIVE SUMMARY

II.1 About the product

Acetylsalicylic acid belongs to the platelet aggregation inhibitors class and has an inhibitory effect on platelet aggregation that persists throughout the platelet life cycle, which is 7-10 days.

Proposed indication:
Acute myocardial infarction. Prophylaxis of cardiovascular complications after acute myocardial infarction and for unstable coronary syndromes (unstable angina pectoris, completed non-Q-wave myocardial infarction) and stable angina pectoris.

Secondary prophylaxis against recurrence of cerebrovascular disease such as TIA (transient ischemic attacks) and RIND (reversible ischemic neurological defect).

Proposed posology:
Acute myocardial infarction: Initially a loading dose of 150-500 mg is given. The loading dose is given as soon as possible after the onset of symptoms.

Prophylaxis of cardiovascular complications after acute myocardial infarction, unstable coronary syndrome (unstable angina pectoris, completing non-Q-wave myocardial infarction), stable angina pectoris: 1 tablet of 75 mg per day.

Prophylaxis of recurrence of cerebrovascular disease: 1 tablet of 75 mg per day.

II.2 General comments on the submitted dossier

The application for Acetysalicylic acid Bluefish, 75 mg, 160 mg, Tablet, is a Generic Art. 10(1) application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and IS as concerned member state (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Trombyl 160mg, tablet authorised in Sweden since 1989, with Pfizer AB as marketing authorisation holder.

The reference product used in the bioequivalence study is Trombyl, 160mg, tablet from Sweden with Pfizer AB as marketing authorisation holder.

European Reference Product (ERP)
A European Reference Product is used in CMS IS: Trombyl, 75mg and 160mg, tablet authorised in Sweden since 1989, with Pfizer AB as marketing authorisation holder.

II.3 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.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is 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 study has been provided. No issues regarding GCP have been identified. The clinical and the bioanalytical facilities were inspected by the WHO in 2011 and in 2015, without any critical findings.

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 acetylsalicylic acid are well known. As acetylsalicylic acid is 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.

Environmental Risk Assessment (ERA)
Since Acetysalicylic acid Bluefish is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Acetylsalicylic acid Bluefish from a non-clinical point of view.

III.3 Clinical aspects

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one of bioequivalence study comparing Acetysalicylic acid Bluefish with the reference product Trombyl.

Absorption: After oral administration, acetylsalicylic acid is rapidly absorbed from the gastrointestinal tract. Maximum plasma concentration is reached after 0.3-2 hours (total salicylate).

Linearity: The pharmacokinetics of ASA is linear within the dose range 75-160 mg.

Elimination: Acetylsalicylic acid is rapidly metabolised to salicylic acid, with a half-life of 15-30 minutes. The elimination of salicylic acid is dose dependent. At daily doses of less than 3 g, the half-life is about 2-4 hours.

Study C12168
Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 24 healthy volunteers, comparing Acetylsalicylic acid Bluefish, 160 mg, tablet with Trombyl, 160 mg, tablet under fasting conditions. Blood samples were collected pre-dose and up to 12 hours post-dose. Plasma concentrations of acetylsalicylic acid (ASA) and the metabolite salicylic acid (SA) were determined with an adequately validated LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 27th April and 10th June 2015.

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

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for Acetylsalicylic acid (ASA), n=21.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**1799.3±275.0**	**2876.4±718.6**	**0.33 0.25-0.67**
Reference	**1744.8±285.7**	**2853.1±869.9**	**0.33 0.25-0.67**
***Ratio (90% CI)**	**103.1 (98.30-108.18)**	**102.5 (94.36-111.44)**	**-**

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 plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} of acetylsalicylic acid, the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

A biowaiver was sought for the additional strength of 75 mg.

Discussion and overall conclusion
The bioequivalence 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) and ICH M13A Guideline on bioequivalence for immediate-release solid oral dosage forms (EMA/CHMP/ICH/953493/2022). The bioanalytical methods were adequately validated.

Absence of studies with the additional strength of 75 mg is acceptable, as all conditions for biowaiver for additional strength, as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled and since the pharmacokinetics of ASA is linear between 75 mg and 160 mg.

Based on the submitted bioequivalence study, Acetylsalicylic acid Bluefish is considered bioequivalent with Trombyl.

Pharmacovigilance system
Proposed MAH : Bluefish Pharmaceuticals AB
The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. 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
No additional pharmacovigilance activities or risk minimisation measures proposed or needed in the RMP. The list of safety concerns is thus empty in line with GVP module V rev 2.

Part II Safety specification

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Part III Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Part VI Summary of the RMP

The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.2 signed 2025-03-12 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 listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

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

IV. BENEFIT RISK ASSESSMENT

The quality of the generic product, Acetysalicylic acid Bluefish, is found adequate. There are no objections to approval of Acetysalicylic acid Bluefish, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. 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

N/A

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to 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

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Acetylsalicylsyra Actavis 75/100/150/160 mg gastro-resistant tablet and Venlafaxine 37.5 mg, 75 mg and 150 mg Capsules.

Content
The applicant has proposed a bridging to a user test carried out on the product Acetylsalicylsyra Actavis 75/100/150/160 mg gastro-resistant tablet. The user test of the Acetylsalicylsyra Actavis

leaflet was assessed and accepted in SE/H/1020/002-005/DC. A comparison between the parent PL and the daughter PL together with a critical discussion hereof has been provided.

Layout
The applicant has proposed a bridging to a user test carried out on the product Venlafaxine 37.5 mg, 75 mg and 150 mg Capsules. The user test of the Venlafaxine leaflet was assessed and accepted in SE/H/1020/002-005/DC. A comparison between the parent PL and the daughter PL (including lay-out) together with a critical discussion hereof has been provided.

The proposed bridging regarding content and layout is considered acceptable.

V.5 Labelling

The approved Labelling is available in the MRI Product Index.

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
-	-	-	-	-	-