LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Tadalafil Bluefish
(tadalafil)

SE/H/2594/01/DC

This module reflects the scientific discussion for the approval of Tadalafil Bluefish. The procedure was finalised on 2025-02-20. 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, a marketing authorisation has been granted for Tadalafil Bluefish, 20 mg, Film-coated tablet.

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

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Tadalafil Bluefish, 20 mg, film-coated 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 AT, DE and NO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is **Cialis**, 20 mg, film-coated tablet, authorised in EU since 2002, with Eli Lilly Nederland B.V. as marketing authorisation holder.

The reference medicinal product authorised in the Union/Member State where the application is made (sharing the indication *PAH* herein applied for by the applicant) is **Adcirca**, 20 mg, film-coated tablet, authorised in EU since 2008 (as Informed consent to Cialis), with Eli Lilly Nederland B.V. as marketing authorisation holder.

The reference product used in the bioequivalence study is **Cialis**, 20 mg, film-coated tablet, from EU with Eli Lilly Nederland B.V. as marketing authorisation holder.

Potential similarity with orphan medicinal products

According to the application form and a check of the Community Register of orphan medicinal products the following medicinal product(s) has/have been designated as orphan medicinal products, but not yet been granted a marketing authorisation in the EU: EU/3/19/2158; EU/3/17/1861; EU/3/21/2538; EU/3/07/443; EU/3/21/2449; EU/3/11/869; EU/3/18/1982; EU/3/18/2130; EU/3/12/967; EU/3/20/2369; EU/3/17/1912; EU/3/07/499; EU/3/05/310; EU/3/04/197; EU/3/16/1638; EU/3/03/173. Added as a 17th orphan designation during national phase: EU/3/24/2972.

The applicant should monitor these products during the entire procedure to check if a marketing authorisation has been granted. In case a marketing authorisation is granted, the applicant should submit a report on similarity (Module 1.7.1) and, if applicable, submit the data to support derogation from orphan market exclusivity (Module 1.7.2).

The applicant has provided a similarity report (Module 1.7.1) due to potential similarity with authorised orphan medicinal product(s) under market exclusivity. However, an updated Module 1.7.1 has been requested due to incorrect information stated regarding the molecular structure of Winrevair. EU/3/20/2369 was authorised under the EU number EU/1/24/1850 as an orphan medicinal product “Winrevair” with orphan market exclusivity starting from 2024-08-27.

Conclusion

The applicant has provided a revised updated similarity report (Module 1.7.1) due to potential similarity with authorised orphan medicinal product under market exclusivity (EU/1/24/1850, Winrevair).

Having considered the arguments presented by the applicant and with reference to Article 8 of Regulation (EC) No 141/2000, Tadalafil Bluefish PAH is considered **not similar** (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to Winrevair.

Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Winrevair in the treatment of *pulmonary arterial hypertension (PAH)*, **does not prevent** the granting of the marketing authorisation of **Tadalafil Bluefish**. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

II. QUALITY ASPECTS

II.1 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.

II.2 Medicinal 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. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of tadalafil are well known. As tadalafil 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 Tadalafil 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 Tadalafil Bluefish from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted two bioequivalence studies comparing Tadalafil 20 film-coated tablets with the reference product Cialis 20 mg film-coated tablets under fasting and fed conditions.

Pharmacokinetic properties of the active substance
Absorption:
Following an oral dose of tadalafil, maximal plasma concentrations occur at approximately 4 hours. The pharmacokinetics of tadalafil is not affected by food, and therefore there are no restrictions with respect to food in the SmPC of the originator.
Linearity:
The pharmacokinetics of tadalafil is linear within the dose range 2.5-20 mg. In the dose range 20 and 40 mg, the pharmacokinetics is non-linear with a less than proportional increase in AUC with increasing dose.
Elimination:
The terminal half-life is 16 hours.

Study 0350-23 (fasting study)
Methods
This was a single-dose, two-way crossover study conducted in 68 healthy volunteers, comparing Tadalafil, 20 mg, film-coated tablet with Cialis, 20 mg, film-coated tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of tadalafil were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-72h} and C_{max}. The study was conducted between 27th Oct and 26th Nov 2023.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.
Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range)for tadalafil, n=60, study 0350-23 (fasted state)

Treatment	**AUC_{0-72h}** ng*h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	10908 ± 3852	354.3 ± 100.1	4.49 (0.67 - 5.0)
Reference	12130 ± 4975	420.3 ± 134.1	4.25 (0.67 - 10.0)
***Ratio (90% CI)**	90.8 (85.74-96.24)	85.0 (80.53-89.63)	-
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_{0-72h} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Study 0351-23 (fed study)
Methods
This was a single-dose, two-way crossover study conducted in 40 healthy volunteers, comparing Tadalafil, 20 mg, film-coated tablet with Cialis, 20 mg, film-coated tablet under fed conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of tadalafil were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-72h} and C_{max}. The study was conducted between 18th Oct and 11th Nov 2023.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 2 below.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for tadalafil, n=38, study 0351-23 (fed state).

Treatment	AUC_{0-72h} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	13377 ± 3681	469.6 ± 95.8	5.00 (2.33 - 6.00)
Reference	13073 ± 3316	456.3 ± 93.0	5.00 (1.67 - 24.0)
***Ratio (90% CI)**	101.8 (97.58-106.10)	102.9 (98.04-108.03)	-
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_{0-72h} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Discussion and overall conclusion
Tadalafil Bluefish is an immediate-release formulation for which a single-dose bioequivalence study is adequate. The product has specific formulation characteristics and studies in both fasted and fed state were conducted which is in accordance with EMA/CHMP/315234/2014 Rev.2*, '*Tadalafil Product-Specific Bioequivalence guidance*'.
The bioequivalence studies 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). The bioanalytical methods were adequately validated.

Based on the submitted bioequivalence studies, Tadalafil Bluefish, 20 mg film-coated tablet is considered bioequivalent with Cialis, 20 mg film-coated tablet.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

Risk Management Plan
The MAH has submitted an updated risk management plan, version 0,2, 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 Tadalafil Bluefish.

The RMP has been updated only to include the proposed/new product name Tadalafil Bluefish. The applicant confirms that no other changes were made to the RMP other than the information related to the product name change.

Part II Safety specification
The proposed summary of safety concerns (see table below) is aligned with the published RMP summary of Adcirca (tadalafil), which is endorsed.

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 applicant has adequately summarised the RMP; the Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.2 signed 2024-11-06 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.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report. For the content, reference is made to a user test carried out on the product Adcirca (assessed and accepted in procedure EMEA/H/C/1021/II/0001). For the layout, reference is made to a user test carried out on the product Venlafaxine 37.5 mg, 75 mg and 150 capsules (assessed and accepted in procedure UK/H/1400/001-3/DC).
The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Tadalafil Bluefish, is found adequate. There are no objections to approval of Tadalafil 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.

With reference to Article 8 of Regulation (EC) No. 141/2000, the current existence of market exclusivity for the orphan medicinal product Winrevair in the treatment of *pulmonary arterial hypertension (PAH)*, does not prevent the granting of the marketing authorisation of Tadalafil Bluefish, and does thereby not affect the above initial recommendation.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A.

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A.

VII. APPROVAL

The decentralised procedure for Tadalafil Bluefish, 20 mg, Film-coated tablet was positively finalised on 2025-02-20.

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Public Assessment Report – Update

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

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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