LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Parakron Forte
(paracetamol)

This module reflects the scientific discussion for the approval of Parakron Forte. The procedure was finalised on 2024-09-03. 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 Parakron Forte, 1 g, Film-coated tablet.

The active substance is paracetamol. 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 Parakron Forte, 1 g, Film-coated tablet, is a hybrid application submitted according to Article 10(3) of Directive 2001/83/EC. The applicant applies for a marketing authorisation in Sweden through a National Procedure.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Panodil, 500 mg, tablet authorised in SE since 1958, with Perrigo Sverige AB as marketing authorisation holder.

Potential similarity with orphan medicinal products

N/A

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 paracetamol are well known. As paracetamol 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 Parakron Forte is intended to substitute other identical products on the market, 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 Parakron Forte from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
No bioequivalence study has been submitted in this application since the applicant applies for a BCS-based biowaiver.

It is generally accepted that paracetamol has complete absorption and can be classified as a BCS class I substance from pharmacokinetic perspective. Paracetamol is not considered to have a narrow therapeutic index in the sense that the acceptance criteria would need to be tightened in a bioequivalence study.

However, according to ICH M9 on biopharmaceutics classification system-based biowaivers (EMA/CHMP/ICH/493213/2018), a drug product is eligible for a BCS-based biowaiver provided that the drug substance(s) satisfy the criteria regarding solubility and permeability (BCS class I and III), the drug product is an immediate-release oral dosage form with systemic action, and the drug product is the **same** dosage form and **strength as the reference product**. This is not fulfilled as the drug product has a different strength compared to the reference product.

Normally, for a BCS-biowaiver, comparison should always be made to the corresponding strength of the reference product. A biowaiver of additional strength should be applied only when the test product has shown bioequivalence to the reference product by means of an *in vivo* bioequivalence study, i.e. not when bioequivalence has been demonstrated via a BCS biowaiver. However, Panodil 1g film-coated tablets are currently deregistered. Nevertheless, in case BCS-biowaiver criteria are fulfilled for applicant's own paracetamol 500 mg film-coated tablets (not included in the current application) and in case the general biowaiver criteria in section 4.1.6 of the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**) are fulfilled between applicant's paracetamol 500 mg and 1 g strength, there would not be any concerns regarding approval of the applied product from a pharmacokinetic perspective.

The BCS-biowaiver criteria for applicant's own paracetamol 500 mg film-coated tablets and the general strength biowaiver criteria between applicant's paracetamol 500 mg and 1 g strength is fulfilled. Thus, the lack of a pharmacokinetic study is acceptable.

Pharmacodynamics
No new data have been submitted. No data are required for an abridged application provided bioequivalence has been satisfactorily demonstrated. This product contains paracetamol. Paracetamol is a well-known, widely used active substance with analgesic and antipyretic effects.

Clinical efficacy
No clinical efficacy and safety studies were submitted, and none are needed. Paracetamol is a well-tolerated and well-known analgesic.

Clinical safety
Paracetamol is generally well tolerated. The principal safety issue is liver toxicity, which is related to dose. Patients suffering from chronic alcoholism or patients treated with barbiturates can be more susceptible to the toxicity of an overdose of paracetamol. The use of paracetamol at high doses for a prolonged period of time has also been associated with renal impairment. In some asthmatic patients sensitive to acetylsalicylic acid, mild bronchospastic reactions have been described with paracetamol.

Risk Management Plan
The MAH has submitted a risk management plan, version 0.1, signed 25 September 2023, 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 Parakron Forte.

Part II Safety specification
The applicant has provided the following summary of safety concerns:

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 0.1 signed signed 25 September 2023, 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 making reference to Paracetamol Evolan 1 g film-coated tablets Diarienr 5.4.1-2016-64901.

Additionally, for the layout, the Applicant refers to their Evolan-design, tested and approved for Natriumklorid Evolan 50 mg, hard capsule, Asp nr 2014-0066, MTnr 50769 (SE/H/2146/MR).

The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product, Paracetamol Evolan, is found adequate. There are no objections to approval of Paracetamol Evolan, from a non-clinical and clinical point of view. The absence of bioequivalence studies is acceptable. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

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

Parakron Forte, 1 g, Film-coated tablet was approved in the national procedure on 2024-09-03.

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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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