LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Paracetamol Medical Valley
(paracetamol)

SE/H/2056/01-02/DC
2019-1376, 2019-1377

This module reflects the scientific discussion for the approval of Paracetamol Medical Valley. The procedure was finalised on 2020-12-16. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Medical Valley Invest AB has applied for a marketing authorisation for Paracetamol Medical Valley, 500 mg, 1000 mg, film-coated tablet. The active substance is paracetamol, which is a well-known and widely used drug and belongs to the group of anilides (ATC code N02BE01). It has analgesic and antipyretic effects but minimal anti-inflammatory effects. It is used for the relief of mild to moderate pain and against fever. The primary mechanism of action might be the inhibition of the prostaglandin synthesis and paracetamol might have central effects but its mechanism of action remains unclear and is the subject of continuing research.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC.

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

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 and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Paracetamol Medical Valley 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 Paracetamol Medical Valley from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

IV.2 Pharmacokinetics

The pharmacokinetics for paracetamol is well known and the information is considered sufficient for a well-known substance.

No bioequivalence study was submitted since a BCS biowaiver was applied for. This is acceptable as paracetamol is considered to be a BCS class I compound. The bridge to the literature supporting efficacy and safety is acceptable.

IV.3 Pharmacodynamics

While treatment with paracetamol is well established, its mode of action is not fully understood. Paracetamol is a weak inhibitor of cyclo-oxygenase-1 and -2, and consequently the prostaglandin synthesis. In has been suggested, central nervous system cyclo-oxygenase is more sensitive for paracetamol than peripheral cyclo-oxygenase and this may explain why paracetamol has an antipyretic and analgesic effect without peripheral anti-inflammatory activity.

The PD characteristics of paracetamol are considered as adequately addressed in the clinical overview.

IV.4 Clinical efficacy

The Applicant has proposed the indication in section 4.1 of the SmPC as follows: symptomatic treatment of headache, toothache, menstrual pain, muscle and joint pain, rheumatic pain, fever during cold and hyperpyrexia. This indication is consistent with the indication included for a number of paracetamol containing medicinal products such as Panodil marketed in SE and DK. Furthermore, the Applicant has submitted a Clinical Overview including literature references together with a sufficient discussion in support the present indication of paracetamol. Overall, the clinical overview on efficacy is considered adequate and proposed indication for paracetamol is acceptable.

IV.5 Clinical safety

Paracetamol is a well-known, widely used active substance that is considered safe when used within the recommended dose range. The submitted Clinical Overview describes, for example, the the incidence of adverse events and safety of paracetamol in adults as well as in paediatric population. Assessment of the studies submitted in the clinical overview did not reveal any new adverse events after paracetamol treatment in adults or children for any indication. Safety aspects related to drug-drug interactions (DDI) and in special population, including patients with renal and hepatic impairment, are presented in detail in the clinical pharmacokinetics section. Overall, the presented overview on safety in the Clinical Overview is considered acceptable.

IV.6 Risk Management Plans

The MAH has submitted a risk management plan (RMP), 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 Paracetamol Medical Valley 500 mg and 1000 mg, film-coated tablets.

Safety specification

Summary table of safety concerns in the updated RMP version 1.2 as proposed by the applicant:

Important identified risks	None
Important potential risks	None
Missing information	None

The safety profile of paracetamol is considered well characterised, there are no additional pharmacovigilance activities or additional risk minimisation measures, and no specific clinical measures to address the risks identified. Paracetamol is available in products with prescription only status. It is also since long widely available in OTC products for perioral or rectal application, some of these even outside pharmacies. It is therefore considered that there should be no important identified risks, no important potential risks, and no missing information items in the summary of safety concerns. As suggested by the MPA, the Applicant has agreed to include no specific items in the summary of safety concerns, which was proposed in the first round. The summary of safety concerns in the RMP version 1.2 is acceptable.

Pharmacovigilance Plan

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

Risk minimisation measures

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

Summary of the RMP

The submitted Risk Management Plan, version 1.2 signed 30 April 2020 is considered acceptable.

IV.7 Discussion on the clinical aspects

The active substance of the medicinal product is not considered a new active substance. Paracetamol has been well-established in medicinal products for the claimed therapeutic indication for several decades in the EU, with recognised efficacy and an acceptable level of safety.

V. USER CONSULTATION

Paracetamol Medical valley 500 mg film-coated tablets
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 PIL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

Paracetamol Medical Valley 1000 mg film-coated tablets
A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Paracetamol Medical valley 500 mg

film-coated tablets (SE/H/2056/01-02/DC). The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The extensive clinical experience with paracetamol is considered to have demonstrated efficacy and an acceptable level of safety in the claimed therapeutic indication. Based on the review of the data on quality, safety and efficacy, the benefit/risk ratio is considered positive and Paracetamol Medical Valley is recommended for approval. Following review of the submitted data, no new safety concerns have been identified. The product information is considered acceptable.

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

N/A

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

N/A

VII. APPROVAL

The decentralised procedure for Paracetamol Medical Valley, 500 mg and 1000 mg, film-coated tablet was positively finalised on 2020-12-16.

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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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