LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Nodevla
(paracetamol)

2019-0549

This module reflects the scientific discussion for the approval of Nodevla. The procedure was finalised on 2020-06-29. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

GlaxoSmithKline Consumer Healthcare A/S has applied for a marketing authorisation for Nodevla, 500 mg, film-coated tablet. The active substance paracetamol is the same as in Alvedon, film-coated tablet, marketed by GlaxoSmithKline Consumer Healthcare A/S, since 1958.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC.

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

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

III.1 Ecotoxicity/environmental risk assessment

Since Nodevla will substitute for other paracetamol-containing products, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

There are no objections to approval of Nodevla from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

The Applicant has submitted clinical pharmacokinetic studies with the test product "Panadol FD" and the reference product "Panadol" and justified that these products are relevant for the product applied for; Nodevla (proposed product) and Alvedon (current product).

The applicant has demonstrated bioequivalence between the test and reference products in the semi-fed state. In the fasting state, the confidence interval for the ratio between test and reference regarding AUC was within the acceptance limits for bioequivalence, whereas the upper limit of the confidence interval for C_{max} was just above the acceptance limits. A slightly higher C_{max} can however be considered safe considering that there are other relative fast absorbed oral paracetamol products on the market.

The applicant has also demonstrated a slightly faster absorption (a somewhat shorter T_{max} and a higher $AUC_{0\text{-}30min}$) for the test product than the reference product, both in fasting and semi-fed state. The test product was shown to disintegrate faster in the stomach. In general, the absorption of both formulations (test and reference) was faster (shorter t_{max}, higher $AUC_{0\text{-}30\ min}$) under fasting conditions than in the fed state. The differences between the formulations were also larger in the study where the patients were in a semi-fed state.

IV.2 Pharmacodynamics

The mechanism of action for paracetamol remains unclear and is the subject of continuing research. The pharmacodynamics of paracetamol is considered adequately summarised in the applicant's Clinical Overview.

IV.3 Clinical efficacy

The Applicant presented two Clinical Efficacy studies (A4000684 and A4000685). Both were single-centre, single dose, randomized (stratified by baseline pain intensity), placebo-controlled, double-blind, double-dummy, parallel group trials. Study A4000684 compared the clinical efficacy of PANADOL tablets (new formula) 1000 mg (2 x 500 mg) versus PANADOL tablets (new formula) 500 mg versus placebo following surgical removal of up to 2 mandibular third molars. Study A4000685 compared clinical efficacy of PANADOL tablets (new formula) 1000 mg (2 x 500 mg) versus standard paracetamol 650 mg versus placebo following surgical removal of up to two mandibular third molars.
The Applicant also presented a review of the published literature about the well-established efficacy of paracetamol in alleviating the symptoms of sore throat, headache, muscle ache, migraine, dysmenorrhoea, dental pain, osteoarthritis, musculoskeletal pain, fever, common cold and flu and earache/otalgia.
The effect profile of paracetamol is well known and no new claims on efficacy have been made from the evidence of the literature review. The review has been considered adequate. The two clinical

efficacy studies were presented as support for clinical efficacy and for justification of the claim for reduction of the time period until pain relief commences from half an hour to 15-20 minutes in section 5.1 of the SmPC. This has been considered acceptable.

IV.4 Clinical safety

Safety was evaluated in the two pivotal PK studies (A1900260 and A1900265), in one scintigraphy study (A1900279) including patients with type II diabetes, in one supporting PK study (A1900385) and two clinical efficacy studies (A4000684 and A4000685) by AE reports, pre- and post-treatment clinical laboratory assessments, and vital signs. The safety profile of paracetamol is well known with known hepatoxicity after overdose or underlying hepatic disease. It is a safe drug as long as it is taken within the recommended dose range and this has been confirmed by the safety evaluation of the presented safety data.

IV.5 Risk Management Plans

Because no change to the list of safety concerns has been made or no new additional pharmacovigilance activity or risk minimisation activity were necessary, there was no need to submit an RMP or an updated RMP as part of an application for this line extension (CMDh/067/2007, Rev.2 October 2015).
The applicant has provided a satisfactory justification for not providing an RMP/updated RMP as part of the application for this line extension.

IV.6 Discussion on the clinical aspects

The benefit/risk balance is considered positive and Nodevla, 500 mg, film-coated tablet, is recommended for approval.

V. USER CONSULTATION

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 Alvedon Novum with Swedish MA nr: 44677. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Based on the review of the data and the Applicant’s response to the questions raised on quality, safety and efficacy, the application for Nodevla, 500 mg, film-coated tablet is considered approvable.
The benefit/risk balance for Nodevla is considered positive. There are no outstanding questions and the product information is considered acceptable.

No need for conditions under Article 21a/22 of Directive 2001/83 has been identified.

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

Nodevla, 500 mg, film-coated tablet was approved in the national procedure on 2020-06-29.

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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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