LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

# Public Assessment Report

# Scientific discussion

# Stasipara 500 mg, 650 mg, 1 g (paracetamol)

# Asp no: 2012-0678, 2012-0679, 2012-0680

# Applicant: E Consult ApS, Denmark

**This module reflects the scientific discussion for the approval of Stasipara. The procedure was finalised at 2012-11-08. For information on changes after this date please refer to the module 'Update'.**

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# I. INTRODUCTION

E Consult ApS has applied for a marketing authorisation for Stasipara, 500 mg, 650 mg and 1 g, film-coated tablets claiming essential similarity to Panodil 500 mg film-coated tablets and Panodil Forte 1 g film-coated tablets, marketed in Sweden by GlaxoSmithKline Consumer Healthcare A/S. The product contains paracetamol as active substance. For approved indications see the Summary of Product Characteristics.

# II. QUALITY ASPECTS

## II.1 Introduction

Stasipara is presented in the form of film-coated tablets containing 500 mg, 650 mg or 1 g of paracetamol. The excipients are maize starch, povidone, pregelatinised starch, stearic acid, talc and Opadry White Y-1-7000. Opadry consists of hypromellose, titanium dioxide and macrogol. The tablets are packed in blisters or containers.

## II.2 Drug Substance

Paracetamol has a monograph in the Ph Eur.

"Drug substance" is a white, or almost white, crystalline powder which is sparingly soluble in water and freely soluble in alcohol. The structure of paracetamol has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

## II.3 Medicinal Product

Stasipara is formulated using excipients described in the current Ph Eur, except for Opadry White Y-1-7000, which is/ controlled according to acceptable *in-house specification*. All raw materials used in the product has demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the active substance.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

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 under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, *with no special storage precautions.*

# III. NON-CLINICAL ASPECTS

## III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

# IV. CLINICAL ASPECTS

## IV.1 Pharmacokinetics

There were no bioequivalence studies submitted with the application. Instead a complete BCS-based biowaiver was suggested.

Depending on the data source paracetamol may be classed as a BCS I or BCS III drug substance. In a study by Rawlins et al, absolute bioavailability was estimated to 0.63, 0.89 and 0.87 after a dose of 500 mg, 1 g and 2000 mg respectively. This is in line with other studies, where absolute bioavailability within the range of 60-80% has been reported (Eandi et al., 1984 and Clements et al., 1984).

Since no metabolism is considered to occur in the gastric or intestinal fluid, urinary excretion data could be used to assess fraction absorbed for paracetamol. In a study by Tukker et al. 1986, the fraction absorbed based on urinary excretion data was > 90% when urine was collected up to 24 hours after dosing. In another study, the fraction absorbed is estimated to 70-76% based on urine collection up to 12 hours after dose administration (Goicoechea et al. 1998). In these studies, paracetamol and some of the metabolites were measured (not exactly the same in the two studies), i.e. neither of the studies used radio-labelled drug substance, but this is considered acceptable.

Thus, depending on the data source paracetamol may be classed as a BCS I or BCS III drug substance, but taken together the data point toward that paracetamol has a fraction absorbed greater or equal to 85% of the dose, which is the cut-off value used in the European guidelines. Thus, paracetamol can be classified as a BCS class I substance from a pharmacokinetic perspective. For a BCS class I substance the difference regarding the excipients between test and reference product are considered acceptable.

Thus BSC biowaiver for the 500 mg strength and the 1 g strength is acceptable from a pharmacokinetic perspective. Since the quality criteria regarding BSC biowaiver is fulfilled no bioequivalence study is necessary for these strengths. For the 650 mg strength, no corresponding strength for the reference product exists and thus it is not possible to compare the compositions. However, since the quality criteria regarding biowaiver for the additional

strength are fulfilled, a bioequivalence study with the 650 mg strength is not considered necessary from a pharmacokinetic perspective.

### IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

## V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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 Nifedipine Alternova (DK/H/767/01-02/II/025) and Paracetamol Pensa (DE/H/2818). The bridging report submitted by the applicant has been found acceptable.

The risk/benefit ratio is considered positive and Stasipara, 500 mg, 650 mg and 1 g, film-coated tablets, is recommended for approval.

## VI. APPROVAL

Stasipara, 500 mg, 650 mg and 1 g, film-coated tablets, was approved in the national procedure on 2012-11-08.

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# Public Assessment Report – Update

| Scope | Procedure number | Product Information affected | Date of start of the procedure | Date of end of procedure | Approval/ non approval | Assessment report attached |
|---|---|---|---|---|---|---|
| | | | | | | Y/N (version) |

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