IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the IMB has granted a marketing authorisation for Non-drowsy sudaplus tablets from McNeil Healthcare (Ireland) limited on 29th June 2011 for Symptomatic relief of nasal congestion when combined with fever and/or pain such as, sore throat, sinus pain or headache in the common cold or influenza.

This application for a marketing authorisation was submitted in accordance with Article 10c of Directive 2001/83/EC and is referred to as an 'informed consent' application. This means that the Marketing Authorisation Holder for Non-drowsy sinutab tablets, an authorised medicinal product in Europe, has permitted the applicant to refer to their dossier to obtain an authorisation for Non-drowsy sudaplus. Non-drowsy sudaplus tablets have the same qualitative and quantitative composition in terms of actives substances and the same pharmaceutical form as Non-drowsy sinutab tablets.

This is an over the counter preparation available only from pharmacies.

The Summary of Product Characteristics for (SPC) for this medicinal product is available on the IMB's website at www.imb.ie

Name of the product: Non-drowsy sudaplus tablets Name(s) of the active substances (INN): Paracetamol 500 mg Pharmacotherapeutic classification (ATC code): Pseudoephedrine HCl 30 mg
Pharmaceutical form and strength(s): Paracetamol & pseudoephedrine HCl
N02BE03 & R01BA02
500 mg & 30 mg
Marketing Authorisation Number(s) in Ireland (PA): PA23490/021/001
Marketing Authorisation Holder: JNTL Consumer Health I (Ireland) Limited

II. QUALITY ASPECTS

II.1. Introduction

This application is for:
Non-drowsy sudaplus tablets
Paracetamol 500mg
Pseudoephedrine hydrochloride 30 mg

II.2 Drug substance

The active substances are paracetamol and pseudoephedrine hydrochloride, established active substances in the European Pharmacopoeia, and are manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements.

II.3 Medicinal product

P.1 Composition

The product is a white, round, biconvex tablet.

The tablet contains paracetamol 500 mg & pseudoephedrine hydrochloride 30 mg as active substances. Other ingredients are microcrystalline cellulose, maize starch, crospovidone, sodium starch glycollate, povidone, stearic acid and magnesium stearate.

Since this application is an informed consent of the Non-drowsy sinutab tablets application, the Quality data in support of this product are identical to the up-to-date Quality data of the non-drowsy sinutab tablet dossier which has been assessed and approved. More detailed Quality comment is not pertinent.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Non-drowsy sudaplus tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is the same as that present in Sinutab PA 823/5/1 on the European market. No new preclinical data have been submitted. This is acceptable for an informed consent application.

III.2 Pharmacology

Preclinical pharmacology studies were not conducted; this is acceptable for an informed consent application.

III.3 Pharmacokinetics

Preclinical pharmacokinetic studies were not conducted; this is acceptable for an informed consent application.

III.4 Toxicology

The Applicant has not conducted toxicology studies; this is acceptable for an informed consent application.
Toxicology is deemed to be the same as the reference as per section 5.3 of the product characteristics:

Mutagenicity

Paracetamol
In vivo mutagenicity tests of paracetamol in mammals are limited and show conflicting results. Therefore, there is insufficient information to determine whether paracetamol poses a mutagenic risk to man.

Paracetamol has been found to be non-mutagenic in bacterial mutagenicity assays, although a clear clastogenic effect has been observed in mammalian cells *in vitro* following exposure to paracetamol (3 and 10 mM for 2 hr).

Pseudoephedrine
The results of a wide range of tests indicate that pseudoephedrine does not post a mutagenic risk to man.

Carcinogenicity

Paracetamol
There is inadequate evidence to determine the carcinogenic potential of paracetamol in humans. A positive association between the use of paracetamol and cancer of the ureter (but not of other sites of the urinary tract) was observed in a case-control study in which approximate lifetime consumption of paracetamol (whether acute or chronic) was estimated. However, other similar studies have failed to demonstrate statistically significant association between paracetamol and cancer of the urinary tract, or paracetamol and renal cell carcinoma.
There is limited evidence for the carcinogenicity of paracetamol in experimental animals. Liver cell tumours can be detected in mice and liver and bladder carcinomas can be detected in rats, following chronic feeding 500 mg/kg/day paracetamol.

Pseudoephedrine
There is insufficient information available to determine whether pseudoephedrine has carcinogenic potential.

Teratogenicity

Paracetamol

There is no information relating to the teratogenic potential paracetamol. In humans, paracetamol crosses the placenta and attains concentrations in the foetal circulation similar to those in the maternal circulation. Intermittent maternal ingestion of therapeutic doses of paracetamol is not associated with teratogenic effects in humans. Paracetamol has been found to be fetotixic to cultured rat embryos.

Pseudoephedrine
Systemic administration of pseudoephedrine, up to 50 times the human daily dosage in rats and up to 35 times the human daily dosage in rabbits did not produce teratogenic effects.

Fertility

Paracetamol
There is no information relating to the effects of paracetamol on human fertility. A significant decrease in testicular weight was observed when male Sprague-Dawley rats were given daily high doses of paracetamol (500 mg/kg body weight/day) orally for 70 days.

Pseudoephedrine
Systemic administration of pseudoephedrine to rats, up to 7 times the human daily dosage in females and 35 times the human daily dosage in males, did not impair fertility or alter foetal morphological development and survival.

III.5 Ecotoxicity/environmental risk assessment

Not applicable

III.6 Discussion on the non-clinical aspects

As this is an informed consent application there is no need to conduct preclinical studies with this medicinal product. The preclinical aspects are the same as stated in the reference SPC non drowsy sinutab.

IV. CLINICAL ASPECTS

IV.1 Introduction

Paracetamol and pseudoephedrine are well known active substances with established efficacy and tolerability. This medicinal hydrochloride product is the same as Non-Drowsy Sinutab on the European market.

The content of the SPC approved during the national/procedure is in accordance with similar active components such as Solpa Sinus PA 678/93/1 marketed by GlaxoSmithKline and UK/H/0587/IA/039.

IV.2 Pharmacokinetics

Additional pharmacokinetic studies have not been conducted as this is an informed consent application.

Paracetamol:

Absorption: The absorption of paracetamol by the oral route is rapid and complete. Maximum plasma concentrations are reached 30 to 60 minutes following ingestion.

Distribution: Paracetamol is distributed rapidly throughout all tissues. Concentrations are comparable in blood saliva and plasma. Protein binding is low.

Metabolism: Paracetamol is metabolised mainly in the liver, following two major metabolic pathways: Glucuronic acid and sulfuric acid conjugates. The latter route is rapidly saturated at doses higher than the therapeutic dosages. A minor route, catalyzed by the Cytocrome P 450 (mostly CYP2E1), results in the formation of an intermediate reagent (N-acetyl-p-benzoquinoneimine) which under normal conditions of use, is rapidly detoxified by glutathione and eliminated in the urine, after conjugation with cysteine and mercapturic acid.
Conversely, when massive intoxication occurs, the quantity of this toxic metabolite is increased.

Elimination: Elimination is essentially through the urine. 90% of the ingested dose is eliminated via the kidneys within 24 hours, principally as glucuronide (60-80%) and sulphate conjugates (20-30%). Less than 5% is eliminated in unchanged form. Elimination half life is about 2 hours.

Physiopathological variations

Renal Insufficiency: In cases of severe renal insufficiency (creatinine clearance lower than 10ml/min) the elimination of paracetamol and its metabolites is delayed.

Elderly subjects: Conjugation capacity is not modified.

Pseudoephedrine:

Absorption: Pseudoephedrine is rapidly and completely absorbed from the gastrointestinal tract after oral administration with no presystemic metabolism. Peak plasma levels are achieved after 1-2 hours.

Distribution: Pseudoephedrine is rapidly distributed throughout the body. No protein binding data are available. The volume of distribution ranges from 2.64 to 3.51 l/kg in both single and multiple dose studies.

Metabolism: There is little metabolism of pseudoephedrine in man with approximately 90% being excreted in the urine unchanged. Approximately 1% is eliminated by hepatic metabolism, by N-demethylation to norpseudoephedrine.

Elimination: The plasma half-life varies from 4.3-7.0 hours in adults.
As a weak base the extent of renal excretion is dependent on urinary pH. At low pH tubular resorption is minimal and urine flow rate will not influence clearance of the drug. At high pH (>7.0) pseudoephedrine is extensively reabsorbed in the renal tubule and renal clearance will depend on urine flow rate.

Renal Insufficiency: Renal impairment will result in increased plasma levels.

Elderly subjects: Elimination capacity is not modified.
A steady state pharmacokinetic interaction study in healthy volunteers has demonstrated that the rate (C_{max}, t_{max}) and extent ($AUC_{0\text{-}6\ hours}$) of absorption from Paracetamol and Pseudoephedrine tablet is equivalent to those of paracetamol alone and of pseudoephedrine alone.
In the same study the median tmax values for the paracetamol and pseudoephedrine components of Paracetamol and Pseudoephedrine tablet were 0.7 hours and 1.2 hours, respectively.

IV.3 Pharmacodynamics

Additional pharmacokinetic studies have not been conducted as this is an informed consent application however this product has similar pharmacodynamics as non drowsy Sinutab ATC Code N02B E51

Non-Drowsy Sudaplus Tablets is a mild to moderate analgesic, antipyretic and decongestant.

The analgesic and antipyretic actions of paracetamol are believed to be due, at least in part, to inhibition of prostaglandin synthesis in the central nervous system. Paracetamol 1 g has been shown to be an effective analgesic and antipyretic.

Pseudoephedrine acts on the alpha adrenergic receptors in the mucosa of the respiratory tract producing vasoconstriction which results is shrinkage of swollen nasal mucous membranes, reduction of nasal congestion and increase in nasal airway patency.

Pseudoephedrine 60 mg has been shown to be an effective nasal decongestant, as measured by nasal airflow, in patients with the common cold and rhinitis.

At therapeutic doses, pseudoephedrine has no clinically significant effect on blood pressure in normotensive patients. Studies in patients with controlled hypertension have demonstrated that pseudoephedrine 60 mg has no, or minimal, effect on blood pressure and does not have sedative effects.

IV.4 Clinical Efficacy

Efficacy studies have not been conducted as this is an informed consent application.

IV.5 Clinical Safety

Safety studies have not been conducted as this is an informed consent application.

The applicant has not proposed a risk management plan, this is acceptable as this is an informed consent application.

The applicant will submit 3 yearly periodic safety update reports for review.

The Marketing Authorisation Holder submitted a set of documents describing the Pharmacovigilance System, including information on the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

IV.6 Discussion on the clinical aspects

As this application is an informed consent application, the applicant has not conducted any efficacy or safety studies. This product is the same as non-drowsy sinutab tablets, which has proven safety and efficacy.

V. OVERALL CONCLUSIONS

Benefit/Risk Assessment and Recommendation
Non-drowsy sudaplus tablets has the same composition as non-drowsy sinutab tablets.

Non-drowsy sinutab tablets is a well-known medicinal product with a proven efficacy and known safety profile.

As this application is an informed consent application no additional preclinical or clinical studies are necessary.

The product information is in line with other similar products containing the same composition.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

Quality
Non-drowsy sudaplus tablets is the same as non-drowsy sinutab tablets. Non-drowsy sinutab tablets is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

The IMB, on the basis of the data submitted considered that non-drowsy sudaplus tablets was the same as the reference product and therefore granted a marketing authorisation.

VI. REVISION DATE

March 2024

VII. UPDATES

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
MA transfer	CRN00DH53	SmPC section 7, 8, 10 Package Leaflet New MA Holder: JNTL Consumer Health I (Ireland) Limited	N/A	01/03/2024

		New PA number: PA23490/021/001		