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Public Assessment Report

Scientific discussion

Paracetamol/Kofein Saneca 500 mg/65 mg Paracetamol/Caffeine

SK/H/0166/001/DC

Date: August 2018

This module reflects the scientific discussion for the approval of Paracetamol/Kofein Saneca 500 mg/65 mg. The procedure was finalised at 23.05.2016. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Paracetamol/Kofein Saneca 500 mg/65 mg, tablets from *Saneca Pharmaceuticals, a.s.*
The product is indicated for*:*
symptomatic treatment of mild to moderate pain, such as headache, including migraine, toothache, neuralgia of different origin, period pain, rheumatic pain, e.g. osteoarthritis, backache, muscle or joint pain, sore throat in influenza or acute upper airways inflammation.
Paracetamol/Kofein Saneca 500 mg/65 mg has also antipyretic effect.

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Paracetamol/Kofein Saneca 500 mg/65 mg are white to off – white oblong tablets, length 16 mm.

II.2 Drug Substance

Paracetamol is analgesic and antipyretic agent without anti-inflammatory effect and with good gastrointestinal tolerability. It is suitable for adults and also for paediatric population. Mechanism of action is likely similar to that of acetylsalicylic acid and depends on inhibition of prostaglandins in central nervous system.
Caffeine potentiates analgesic effect of paracetamol by the stimulation of central nervous system and can relieve the depression which is often accompanied by pain.
Both drug substances, paracetamol and caffeine, are described in the Ph.Eur. Analytical procedures for paracetamol and caffeine are performed in compliance with Ph.Eur monograph. For both active substances valid CEP certificates issued by EDQM have been presented.
Specifications for drug substance product are adequately drawn up.
Stability studies have been performed with paracetamol and caffeine. No significant changes in any parameters were observed.

II.3 Medicinal Product

Both drug substances, paracetamol and caffeine, are of pharmacopoeial quality. The development of the product has been described; the role and choice of the excipients have been explained. For each of the excipients, compliance with the respective Ph Eur monograph has been provided.

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on 3 batches. The batch analysis results show that the finished products meet the specifications proposed.

Dissolution profiles of Paracetamol/Kofein Saneca 500 mg/65 mg and reference product Panadol Extra in three different media have been submitted. The results show that obtained dissolution profiles in all tested media are almost identical. Applicant submitted additional data regarding discriminatory power of dissolution method which was not adequately proven during the first assessment of documentation. These data confirmed discriminatory nature of the proposed dissolution method.
The conditions used in the stability studies are according to the ICH stability guideline. Applicant supplemented the results of stability testing of 9 months which comply with the specification during the stability testing. According to the new submitted data from the manufacturing site Saneca Pharmaceuticals, the proposed shelf-life of 60 months with no special storage conditions required for the drug product is considered as acceptable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of paracetamol and caffeine are well known. As paracetamol and caffeine is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Paracetamol/Caffeine is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

Paracetamol is analgesic and antipyretic agent without anti-inflammatory effect and with good gastrointestinal tolerability. Caffeine potentiates analgesic effect of paracetamol by the stimulation of central nervous system and can relieve the depression which is often accompanied by pain.
Pharmacotherapeutic group: paracetamol, combinations excluding psycholeptics
ATC code: N02BE51

IV.2 Pharmacokinetics

Bioequivalence studies

To support the generic application, the applicant has submitted report of one bioequivalence study which was open label, two-period, two-sequence, two-way crossover, controlled, randomized, single dose bioequivalence study of PAPCO 500 mg/65 mg tablets (test product) vs. equal dose of Panadol Extra 500 mg/65 mg film-coated tablets (reference product) in healthy male and female volunteers under fasting conditions.

Data given on test and reference product is sufficient; batch size of the test product meets the criteria given. Certificates of analysis were provided and the difference in content of active substance between reference and test product is less than 5.0%.

The bioequivalence between PAPCO, medicinal product by PRO.MED.CS. Praha Czech Republic, and the reference product Panadol Extra by MAH GlaxoSmithKline Dungarvan Ltd. has been shown.
Clarification regarding connection between tested product PAPCO by PRO.MED.CS.Praha Czech Republic and to-be-marketed product by Saneca was submitted.

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence study Paracetamol/Kofein Saneca 500 mg/65 mg is considered bioequivalent with Panadol Extra.

IV.3 Pharmacodynamics

Paracetamol is analgesic and antipyretic agent without anti-inflammatory effect and with good gastrointestinal tolerability. It is suitable for adults and also for paediatric population. Mechanism of action is likely similar to that of acetylsalicylic acid and depends on inhibition of prostaglandins in central nervous system.
Absence of prostaglandin peripheral inhibition ensures paracetamol important pharmacologic properties such as maintaning of protective prostaglandins in gastointestinal tract. Paracetamol is therefore suitable mainly in patients with anamnesis of disease or in patients receiving other treatment where is inhibition of peripheral prostaglandins unwanted (e.g patients with anamnesis of gastrointestinal bleeding or elderly).
Analgesic effect of paracetamol after single dose 0.5–1 g lasts for 3–6 hours, antipyretic effect lasts for 3–4 hours. Both effects are comparable to acetylsalicylic acid taken at same doses.
Caffeine potentiates analgesic effect of paracetamol by the stimulation of central nervous system and can relieve the depression which is often accompanied by pain.
Metaanalysis of 30 clinical trials with analgesics and caffeine which included 6 trials with different doses of paracetamol and caffeine showed that combination paracetamol and caffeine is 1.37-times more effective than paracetamol alone ($p<0.05$).

IV.4 Risk Management Plan

The MAH has submitted a risk management plan, 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/Kofein Saneca 500 mg/65 mg.

Summary table of safety concerns is summarized in the table below, the missing safety concern “hepatotoxicity” was added into the list of Important identified risks.

Table 1: Summary table of safety concerns

Important identified risks	Use of paracetamol in hepatic impairment Alcohol abuse Severe haemolytic anaemia Use in children under 12 years Hepatotoxicity
Important potential risks	Use in patients with renal impairment Concomitant use with oral anticoagulants

	Concomitant use with different hepatotoxic substances Concomitant use with hepatic enzyme inducers Use in patients with glucose-6-phosphate dehydrogenase deficiency Overdose Use in pregnant and breast-feeding women
Missing information	Effect on fertility

The following updated Summary of Risk Minimisation Measures by safety concerns was submitted.

Table 2: Summary table of risk minimisation measures

Safety Concern	**Routine Risk Minimisation Measures**
Use of paracetamol in hepatic impairment	Risk minimisation activities consist to describe in relevant section of the SmPC relevant information to minimise the risk: *Section 4.2 Posology and method of administration* Posology *Hepatic impairment* Patients with mild to moderate liver impairment should take this medicinal product with caution. Patients with severe liver impairment should not take this medicinal product. *Section 4.3 Contraindications* - severe hepatic impairment, acute hepatitis *Section 4.4 Special warnings and precautions for use* Regular monitoring of liver function is recommended in patients with mild to moderate liver impairment and in patients on long-term high doses of paracetamol therapy. Risk of overdose is higher in patients with liver disease. *Section 4.8 Undesirable effects* Paracetamol Hepatobiliary disorders *Rare*: abnormal liver tests, liver failure, hepatic necrosis, jaundice *Pack size*
Alcohol abuse	Risk minimisation activities consist to describe in relevant section of the SmPC relevant information to minimise the risk: *Section 4.3 Contraindications* - alcohol abuse *Section 4.4 Special warnings and precautions for use* Long-term alcohol abuse significantly increases the risk of paracetamol hepatotoxicity. The highest risk is in chronic alcoholics with short-term abstinence (12 hours). Alcohol consumption should be avoided during the treatment with < invented name>. *Pack size*
Severe haemolytic anaemia	Risk minimisation activities consist to describe in relevant section of the SmPC relevant information to minimise the risk: *Section 4.3 Contraindications* - severe haemolytic anaemia *Section 4.8 Undesirable effects* Paracetamol Blood and lymphatic disorders *Rare*: platelet disorders, stem cell disorders, hemolytic anemia *Pack size*
Use in children under 12 years	Risk minimisation activities consist to describe in relevant section of the SmPC relevant

Safety Concern	Routine Risk Minimisation Measures
	information to minimise the risk: *Section 4.2 Posology and method of administration* Posology Medicinal product is not recommended for children under 12 years. *Section 4.4 Special warnings and precautions for use* < invented name> is not recommended for children under 12 years. *Pack size*
Hepatotoxicity	Risk minimisation activities consist to describe in relevant section of the SmPC relevant information to minimise the risk: *Section 4.4 Special warnings and precautions for use* Paracetamol can be hepatotoxic in doses exceeding 6–8 g daily. According to post-marketing experiences with paracetamol hepatotoxicity can occur also at lower doses or in short-term use in patients without previous liver function impairment if alcohol, hepatic inductors or other agents toxic for the liver are coactive (see section 4.5).
Use in patients with renal impairment	Risk minimisation activities consist to describe in relevant section of the SmPC relevant information to minimise the risk: *Section 4.2 Posology and method of administration* Posology *Renal impairment* Followind dosage adjustment is necessary in case of renal impairment: • at glomerular filtration rate 50 – 10 ml/min 1 tablet is taken every 6 hours; • at glomerula filtration rate lower than 10 ml/min 1 tablet is taken every 8 hours. *Section 4.4 Special warnings and precautions for use* Caution is necessary also in patients with renal impairment, gradual dose adjustment is recommended (see section 4.2). Renal insufficiency cannot be excluded during long-term treatment with <invented name>. *Pack size*
Concomitant use with oral anticoagulants	Risk minimisation activities consist to describe in relevant section of the SmPC relevant information to minimise the risk: *Section 4.4 Special warnings and precautions for use* The prothrombin time should be monitored in patients treated with oral anticoagulants and higher doses of paracetamol. *Section 4.5 Interaction with other medicinal products and other forms of interaction* The anticoagulant effect of warfarine or other coumarines may be enhanced by prolonged regular daily use of paracetamol with increased risk of bleeding. Occasional intake has no significant effect. *Pack size*
Concomitant use with different hepatotoxic substances	Risk minimisation activities consist to describe in relevant section of the SmPC relevant information to minimise the risk: *Section 4.5 Interaction with other medicinal products and other forms of interaction* Co-administration of paracetamol and isoniazid can increase the risk of hepatotoxicity. The development of neutropenia and hepatotoxicity has been reported in concomitant use of paracetamol and zidovudine. should be used after careful consideration of risk/benefit ratio. Hepatotoxic substances can increase the risk of accumulation and overdose by paracetamol. Pack size
Concomitant use with hepatic enzyme inducers	Risk minimisation activities consist to describe in relevant section of the SmPC relevant information to minimise the risk: *Section 4.5 Interaction with other medicinal products and other forms of interaction* Concomitant use with hepatic enzyme inducers, e.g barbiturates, monoamine oxidase inhibitors, tricyclic antidepressants, St. John´s Wort, antiepileptics (beside glutethimide, phenobarbital, phenytoin, carbamazepine) and rifampicin - paracetamol doses that are otherwise safe, can lead to hepatic impairment. *Pack size*
Use in patients with glucose-6-phosphate dehydrogenase deficiency	Risk minimisation activities consist to describe in relevant section of the SmPC relevant information to minimise the risk: *Section 4.4 Special warnings and precautions for use*

Safety Concern	Routine Risk Minimisation Measures
	Increased caution is necessary in patients with glucose-6- phosphate dehydrogenase deficiency. *Pack size*
Overdose	Risk minimisation activities consist to describe in relevant section of the SmPC relevant information to minimise the risk: *Section 4.4 Special warnings and precautions for use* Risk of overdose is higher in patients with liver disease. Patients should be warned not to exceed recommended dose and not to take other products containing paracetamol. *Section 4.5 Interaction with other medicinal products and other forms of interaction* Hepatotoxic substances can increase the risk of accumulation and overdose by paracetamol. *Section 4.9 Overdose* Symptoms Overdose by relatively low doses of paracetamol (8 - 15 g depending on the body weight of patient) can lead to severe hepatic impairment and sometimes to acute renal tubular necrosis. Symptoms of paracetamol overdose in the first 24 hours may include nausea, vomiting, loss of appetite, sweating and abdominal pain. Symptoms of hepatic failure may occur within 12 - 24 hours after intake of the drug. Abnormalities of glucose metabolism, metabolic acidosis, hemorrhage and hypotension may occur. Acute renal failure with acute tubularbsence of severe liver impairment. Pancreatitis and cardiac arrhythmias have been reported. In severe poisoning, hepatic faulire may progress to encephalopathy, coma and death. Prothrombin time prolongation is one of the indicator of impaired liver function and therefore its monitoring is recommended. Patients taking enzyme inducers (carbamazepine, phenytoin, barbiturates, rifampicin) or with alcohol abuse in history, are more prone to hepatic None proposed Document Page 24 of 57 Product: Paracetamol/Kofein 500 mg/65 mg Document: 1.8.2 Risk-management System Saneca Pharmaceuticals a.s. CONFIDENTIAL Paracetamol/Kofein Saneca 500 mg/65 mg RMP ver. 01 Part I: Product(s) Overview Page 25/57 Safety concern Routine risk minimisation measures Additional risk minimisation measures damage. Management Immediate hospitalisation is essential. Induction of vomiting, gastric lavage should be indicated in patients who have taken paracetamol in the preceding 4 hours. Thereafter methionine (2.5 g orally) or specific antidote should be administered. Treatment with activated charcoal in order to decrease gastrointestinal resorption is questionable. It is recommended to monitor plasma concentrations of paracetamol. Specific antidotum Nacetylcysteine should be administered within 8 – 15 hours after paracetamol overdose. Efficacy declines progressively after this time, but N- acetylcysteine may prvide some benefit up to and possibly beyond 24 hours. Nacetylcysteine is administered to adults and children i.v. in 5% glucose infusion with initial dose 150 mg/kg over 15 minutes. Initial infusion id followed by a continious infusion of 50 mg/kg of N-acetylcysteine in 5 % glucose over the next 4 hours. Subsequently, continious infusion of 100 mg/kg of N-acetylcysteine over the next 16 – 20 hours should be administered. N-acetylcysteine can be used also orally , 70 – 140 mg/kg three times aday within 10 hours after paracetamol overdose. In case of very severe intoxication hemodialysis or hemoperfusion is possible. High doses of caffeine can induce headache, tremor, nervousness and irritability. *Pack size*
Use in pregnant and breast- feeding women	Risk minimisation activities consist to describe in relevant section of the SmPC relevant information to minimise the risk: *Section 4.6 Fertility, pregnancy and lactation* Pregnancy Epidemiologic studies conducted during pregnancy have not shown harmful effects of paracetamol and caffeine taken within recommended doses. Combination paracetamol and caffeine is not recommended during pregnancy because of increased risk of spontanneous abortion connected with caffeine consumption. It is not recommended to take during pregnancy. Lactation Paracetamol is excreted in breast milk, but in amounts that are not clinically significant. Paracetamol or its metabolites have not been established in urine of breast-fed infant. Patologic changes to infants have not been reported. Caffeine is excreted in breast milk and may have stimulatory effect to breast-feeded child, but significant intoxication has not been shown. It is not recommended to take during breast-feeding. *Pack size*
Effect on fertility	Risk minimisation activities consist to describe in relevant section of the SmPC relevant information to minimise the risk: *Section 4.6 Fertility, pregnancy and lactation*

Safety Concern	Routine Risk Minimisation Measures
	Fertility No relevant data are available. *Pack size*

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 PAPCO. Applicant also submitted Outcome Report regarding of user testing of the parent PL for PAPCO. On the basis of Outcome Report the parent PL was tested successfully.
The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit risk assessment was considered positive. Therefore the RMS and CMS recommended approval of Paracetamol/Kofein Saneca 500 mg/65 mg.