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Public Assessment Report

Scientific discussion

Paracetamol/Kofein Xantis 1000 mg/130 mg tablety

Paracetamol/Caffeine

SK/H/0166/003/DC

Date: July 2018

This module reflects the scientific discussion for the approval of Paracetamol/Kofein Xantis 1000 mg/130 mg tablety. The procedure was finalised at 26.06.2018. 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 Xantis 1000 mg/130 mg tablety
tablets from *Xantis Pharma Limited, Cyprus.*
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 Xantis 1000 mg/130 mg tablety 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(3) of Directive 2001/83/EC."

II. QUALITY ASPECTS

II.1 Introduction

Paracetamol/Kofein Xantis 1000 mg/130 mg tablety are white to off-white, oval tablets, with scored line on both sides, length within 22 mm – 23 mm.
Tablet can be divided into equal doses.

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

The development of the product has been described, the choice of excipients is justified and their functions 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 two

batches. The batch analysis results show that the finished products meet the specifications proposed.

The developed product is a tablet containing paracetamol and caffeine. The excipients are comparable with the reference product Panadol Extra film coated tablets and additional excipients (sweeteners, lubricant and flavour) with no influence on bioavailability.

The proposed shelf-life is 36 months with no storage conditions. The proposed shelf-life is 36 months is acceptable on the basis of submitted results supported by stability results of the lower strength. The product needs no special storage conditions.

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/Kofein Xantis 1000 mg/130 mg tablety 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 study
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.

Paracetamol/Kofein Xantis 1000 mg/130 mg tablets – submitted one bioequivalence study with lower strength. Concerning this pharmaceutical form of the proposed medicinal product, this is acceptable. The product PAPCO 500 mg/65 mg tablets is identical to Paracetamol/Kofein Xantis 500 mg/65 mg tablets.

Product	Dissolution medium	Dissolved amount of paracetamol (%, n = 12)					Factor similarity f2 ≥ 50
		5 min	10 min	15 min	20 min	30 min	
PAPCO 500 mg/65 mg, BN 07-090909; bio-batch	0.1 M hydrochloric acid	37.2	65.0	**88.6**	97.6	98.2	f2 test is unnecessary > 85 % dissolved amount in 15 minutes
Paracetamol/Kofein Xantis 1000 mg/130 mg, tablets, BN 02020615		42.3	69.0	**90.1**	95.9	97.4	
PAPCO 500 mg/65 mg, BN 07-090909; bio-batch	phosphate buffer pH = 4.5	48.2	84.3	**98.0**	99.2	99.4	f2 test is unnecessary > 85 % dissolved amount in 15 minutes
Paracetamol/Kofein Xantis 1000 mg/130 mg, tablets, BN 02020615		56.1	88.8	**96.7**	96.7	96.9	
PAPCO 500 mg/65 mg, BN 07-090909; bio-batch	phosphate buffer pH = 6.8	43.7	81.1	**96.9**	99.2	99.6	f2 test is unnecessary > 85 % dissolved amount in 15 minutes
Paracetamol/Kofein Xantis 1000 mg/130 mg, tablets, BN 02020615		44.7	73.2	**91.3**	97.2	97.8	

Product	Dissolution medium	Dissolved amount of caffeine (%, n = 12)					Factor similarity f2 ≥ 50
		5 min	10 min	15 min	20 min	30 min	
PAPCO 500 mg/65 mg, BN 07-090909; bio-batch	0.1 M hydrochloric acid	37.8	65.2	**89.7**	98.9	99.3	f2 test is unnecessary > 85 % dissolved amount in 15 minutes
Paracetamol/Kofein Xantis 1000 mg/130 mg, tablets, BN 02020615		39.0	66.5	**89.4**	95.5	97.5	
PAPCO 500 mg/65 mg, BN 07-090909; bio-batch	phosphate buffer pH = 4.5	46.2	82.9	**97.0**	97.6	97.5	f2 test is unnecessary > 85 % dissolved amount in 15 minutes
Paracetamol/Kofein Xantis 1000 mg/130 mg, tablets, BN 02020615		52.4	87.1	**95.4**	95.3	95.4	
PAPCO 500 mg/65 mg, BN 07-090909; bio-batch	phosphate buffer pH = 6.8	40.0	78.8	**95.8**	97.5	97.6	f2 test is unnecessary > 85 % dissolved amount in 15 minutes
Paracetamol/Kofein Xantis 1000 mg/130 mg, tablets, BN 02020615		43.2	73.0	**92.1**	98.3	98.8	

There were submitted all necessary data to grant biowaiver for additional strength. Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev1) states, that "For products with linear pharmacokinetics and where the drug substance is highly soluble (see Appendix III), selection of a lower strength than the highest is also acceptable." Indeed, paracetamol and caffeine are highly soluble substances, therefore, biowaiver for strength 1000 mg/130 mg is acceptable.

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%.

According to the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), the adequacy of waiving additional in vivo bioequivalence testing should be confirmed by in vitro dissolution data as it is described in Section 4.2. of the Guideline. In case of in vitro dissolution tests in support of biowaiver of strengths, dissolution should be investigated at different pH values and the similarity of in vitro dissolution should be demonstrated at all conditions within the applied product series. According to the Appendix I of the Guideline, test methods should be developed product related based on general and/or specific pharmacopoeial requirements. In case those requirements are shown to be unsatisfactory and/or do not reflect the in vivo dissolution (i.e. biorelevance) alternative methods can be considered that are discriminatory and able to differentiate between batches with acceptable and non-acceptable performance of the product in vivo. Thus, there is no information about the stirring speed required for dissolution tests in support of biowaiver of strengths.
On the other hand, the dissolution conditions stated to be usually 50 rpm for paddle apparatus are defined in the Appendix III of the Guideline which deals with the BCS-Biowaiver, i.e. the biowaiver based on the characteristics of the drug substance when no batch is used in BE study. However, this Application proposes the waiving in vivo bioequivalence testing based on the biowiaver of strengths.

According to the Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action (EMA/CHMP/CVMP/QWP/336031/2017), an increase of the stirring speed may be considered in case of over-discriminatory conditions towards in vivo performance. Since the in-vitro dissolution profiles of the reference and test products used in bioequivalence study were not similar using stirring speed of 50 rpm, as is demonstrated in Tables below, the stirring speed of 50 rpm is over-discriminative towards in vivo performance. Thus, the proposed dissolution method (i.e. stirring speed of 75 rpm) justified.

Table 1 Comparative dissolution profiles of different rotation speeds (paracetamol)

Tablets	**Speed**	**% of dissolved amount of paracetamol**										f_2
		5 min		10 min		15 min		20 min		30 min		
		Average	SD	Average	SD	Average	SD	Average	SD	Average	SD	
Papco 500 mg/65 mg, BN 06-080909, PRO.MED.CS	50 rpm	22.9	2.22	45.2	3.52	62.6	3.70	78.0	4.4	96.1	1.18	**36.0**
PANADOL EXTRA, BN 0807777-08H23	50 rpm	32.9	6.59	64.9	10.64	87.0	8.53	96.5	3.19	99.7	0.98	
Papco 500 mg/65 mg, BN 06-080909, PRO.MED.CS	75 rpm	32.8	2.54	62.9	2.46	88.3	2.51	97.0	2.92	97.2	3.02	**similar > 85 % in 15 minutes**
PANADOL EXTRA, BN 0807777-08H23	75 rpm	44.3	5.27	78.9	5.91	96.4	1.29	98.1	1.22	98.8	1.34	
Papco 500 mg/65 mg, BN 06-080909, PRO.MED.CS	100 rpm	50.8	1.64	87.1	2.30	98.5	0.87	98.8	0.43	98.5	0.86	**similar > 85 % in 15 minutes**
PANADOL EXTRA, BN 0807777-08H23	100 rpm	55.9	5.49	92.8	4.49	99.1	2.04	99.8	1.11	100.0	1.33	

Table 2 Comparative dissolution profiles of different rotation speeds (caffeine)

Tablets	**Speed**	**% of dissolved amount of caffeine**										f_2
		5 min		10 min		15 min		20 min		30 min		
		Average	SD	Average	SD	Average	SD	Average	SD	Average	SD	
Papco 500 mg/65 mg, BN 06-080909, PRO.MED.CS	50 rpm	21.5	1.91	42.8	3.32	61.0	4.44	78.4	4.63	98.8	3.03	**30.0**
PANADOL EXTRA, BN 0807777-08H23	50 rpm	34.0	8.24	69.4	13.37	92.9	10.59	101.6	5.15	103.9	2.69	
Papco 500 mg/65 mg, BN 06-080909, PRO.MED.CS	75 rpm	31.5	1.08	62.0	1.59	89.1	1.27	98.6	1.08	98.9	0.76	**similar > 85 % in 15 minutes**
PANADOL EXTRA, BN 0807777-08H23	75 rpm	46.0	5.5	83.6	6.2	102.3	2.27	103.3	1.62	103.5	1.87	
Papco 500 mg/65 mg, BN 06-080909, PRO.MED.CS	100 rpm	52.1	1.17	89.9	1.34	103.5	2.99	103.8	3.04	103.5	2.89	**similar > 85 % in 15 minutes**
PANADOL EXTRA, BN 0807777-08H23	100 rpm	59.1	6.42	97.4	5.53	102.7	2.79	103.0	2.33	103.0	1.89	

The results of study PRCF-BESD-01-PMD/09 with 500 mg/65 mg formulation can be extrapolated to other strengths 1000 mg/130 mg tablets, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

The justification for BCS (Biopharmaceutics Classification System) - based biowaiver can be accepted.

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 Xantis 1000 mg/130 mg tablets.

Safety specification
The summary of safety concerns proposed by the Applicant in updated version 02.01 of the RMP:

Table 1. Summary of safety concerns

Summary of safety concerns	
Important identified risks	Use of paracetamol in hepatic impairment Severe haemolytic anaemia Hepatotoxicity Severe skin reactions Overdose (non-intentional and intentional)
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 Use in pregnant and breast-feeding women
Missing information	Use in children under 15 years old or weight under 50 kg[1] Effect on fertility

PharmacovigilancePlan
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.

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 *Paracetamol Caffeine 500mg/65mg tablets*. 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 Xantis 1000mg/130 mg tablety.