COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Kruidvat Paracetamol 500 mg, tablets

(paracetamol)

NL/H/4264/001/MR

Date: 18 April 2019

This module reflects the scientific discussion for the approval of Kruidvat Paracetamol 500 mg, tablets. The procedure was finalised at 24 April 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
NAC	N-acetylcysteine
NAPQI	N-acetyl-P-benzoquinoneimine
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Kruidvat Paracetamol 500 mg, tablets from Apotex Europe BV.

The product is indicated for symptomatic treatment of mild to moderate pain and/or fever.

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

The concerned member state (CMS) involved in this procedure was Belgium.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC. The application is a so called bibliographic application based on the well-established medicinal use of paracetamol.

II. QUALITY ASPECTS

II.1 Introduction

The product is a (almost) white, round tablet with a score line on one side and the inscription “PARACETAMOL” on the other. The tablet can be divided in equal doses.

Each tablet contains as active substance 500 mg of paracetamol.

The tablets are packed in blister packs. The blister strip is made of white PVC foil and aluminium foil.

The excipients are maize starch, gelatin, croscarmellose sodium and magnesium stearate.

II.2 Drug Substance

The active substance is paracetamol, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white, crystalline powder, which is sparingly soluble in water.

The CEP procedure is used for all manufacturers of the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This

procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification of the MAH is in accordance with the Ph.Eur. monograph and the additional information provided on the CEPs. Batch analytical data demonstrating compliance with this specification have been provided for batches from all manufacturers.

Stability of drug substance
On the basis of the CEP a retest period of five years is acceptable for one manufacturer. For the other manufacturers a retest period of four years is acceptable. Assessment thereof was part of granting the CEPs and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. Information and dissolution data at various pH values for both the product for registration and several products from the EU market have been included (generic and innovator products). The influence of differences in particle size of the drug substance on the dissolution characteristics has not been examined. Pharmaceutical development has been adequately performed.

Manufacturing process
For the manufacturing of the tablets, the wet granulation process was selected. The product is manufactured using conventional manufacturing techniques. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients
The excipients all comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, mass, identification, uniformity of dosage units, related substances, assay, dissolution, disintegration, subdivision of tablets and microbial contamination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product has been provided for three batches of commercial batch size stored at 25°C/60% RH (54 months), 30°C/65% RH (54 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC-Al blisters.
The stability results show compliance to the specification. On basis of the data submitted, a shelf life was granted of five years. The labelled storage condition is store below 30°C. Photostability of the drug product is adequately demonstrated.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

For gelatin scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Kruidvat Paracetamol 500 mg has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

Paracetamol belongs to the category of non-narcotic non-steroidal anti-inflammatory drugs. It is the active metabolite of phenacetin, a so called coal-tar analgesic. Paracetamol is used to treat pain, inflammation, hyperuricemia and gout. It is also indicated for pain relief in patients with non-inflammatory osteoarthritis. It is well tolerated and has a low incidence of gastrointestinal side effects. It is used as a common house-hold analgesic. When taken at recommended doses it has an excellent safety profile, notably lacking the gastrointestinal (GI) side effects of aspirin and ibuprofen.

Paracetamol would act as a pro-drug, with the active metabolite (AM404) being formed in the brain through conjugation of the deacetylated derivative of paracetamol (p-aminophenol) with arachidonic acid, by the action of fatty acid amide hydrolase (FAAH). At

analgesic doses of paracetamol, AM404 that is formed in rat brain regions expressing high levels of FAAH, can indirectly activate CB1 receptors and directly activate TRPV1 receptors. Interestingly, in brain regions with high expression of FAAH, both TRPV1 and CB1 receptors are also found (mesencephalic trigeminal nucleus, primary sensory neurons).

After administration of paracetamol at 300 mg/kg to rats, the brain concentration of AM404 has been found to be 10.3 ± 1.9 pmol/g tissue wet weight. Assuming an even distribution of AM404 in brain, this would correspond to a tissue concentration of about 10 nM. At this concentration AM404 activates both rat and human TRPV1 receptors, while significant COX-1 and COX-2 inhibition and prostaglandin E2 formation reduction are obtained at micromolar concentrations. It is of course possible (but not demonstrated) that higher concentrations of AM404 are formed in CNS regions expressing high levels of FAAH, such as neuronal somata and dendrites of mesencephalic trigeminal nucleus, layer V of the somatosensory cortex, Purkinje cells of the cerebellar cortex and olfactory glomeruli (Egertova et al., 2003). This would lead to a local significant inhibition of COX activities that could contribute to the effect of paracetamol. At the present time this possibility remains speculative.

III.2 Pharmacokinetics

Paracetamol is rapidly and most completely absorbed from the GI tract. Absorption is by passive diffusion with first-order kinetics and occurs mainly in the small intestine; the rate of absorption therefore depends on the gastric emptying rate. Over all, paracetamol is rapidly and completely absorbed, although systemic bioavailabity after oral administration is incomplete owing to first-pass metabolism. Paracetamol is rapidly and uniformly distributed throughout body tissues; it achieves a tissue: plasma concentration ratio of unity in most tissues except for fat and cerebrospinal fluid. Following oral administration of acetaminophen, peak plasma concentrations are attained within 10 to 60 min.

Following usual oral doses, approximately 25% of paracetamol is metabolized on the first passage through the liver. It is metabolised by microsomal enzymes in the liver, with 85%-90% of the drug undergoing glucuronidation and sulfation to inactive metabolites that are eliminated in the urine. A fraction usually ranging from 5 to 15% is oxidised by CYP2E1, CYP1A2, CYP3A4, and CYP2A6 subfamilies of the P450 mixed-function oxidase system, resulting in the formation of the highly reactive N-acetyl-P-benzoquinoneimine (NAPQI). Glutathione quickly combines with this intermediate, and the resulting complex is then converted to non-toxic cysteine or mercaptate conjugates, which are eliminated in urine. Only 1 to 4% of paracetamol is excreted unchanged in the urine. The metabolic products are excreted mainly by the kidney. The urinary clearance of paracetamol is 13.5 l/h. Elimination occurs almost entirely through the kidneys.

Paracetamol crosses the placenta and is present in breastmilk.

III.3 Toxicology

Paracetamol is a well-established drug and toxicological properties of paracetamol are well known. As paracetamol is a widely used, well-known active substance, the MAH has not provided additional studies and further studies are not required.

In animal studies investigating the acute, sub chronic and chronic toxicity of paracetamol in the rat and mouse, gastrointestinal lesions, blood count changes, degeneration of the hepatic and renal parenchyma and necrosis were observed. These changes are, on the one hand, attributed to the mechanism of action and, on the other, to the metabolism of paracetamol. The metabolites that are probably responsible for the toxic effects and the corresponding organic changes have also been found in humans. Moreover, during long term use (i.e. one year) very rare cases of reversible chronic aggressive hepatitis have been described in the range of maximum therapeutic doses. At sub toxic doses, symptoms of intoxication can occur following a 3-week intake period. Paracetamol should therefore not be administered over a long period of time or at high doses.

Extensive investigations showed no evidence of any relevant genotoxic risk of paracetamol in the therapeutic, i.e. non-toxic, dose range.

Long-term studies in rats and mice yielded no evidence on relevant carcinogenic effects at non-hepatotoxic dosages of paracetamol.

Paracetamol crosses the placental barrier. Animal studies and clinical experience to date have not indicated any teratogenic potential.

With respect to the composition of the product under consideration the following seems of relevance for the toxicological evaluation. The excipients maize starch, gelatin, croscarmellose sodium, magnesium stearate and purified water are well defined pharmaceutical excipients, all of pharmacopoeial grade that are widely used in tablet manufacturing, having a very low or even negligible risk with respect to their toxic potential. With respect to the synthetic process and impurity profile of the paracetamol raw material used for the product under consideration, specific information is included in the pharmaceutical dossier in the form of CEPs of the active ingredient manufacturers. Impurities are tested and limited in accordance with Ph.Eur monographs. Finished product specifications are according British Pharmacopoeia (BP).

III.4 Ecotoxicity/environmental risk assessment (ERA)

For this well established use application a formal Environmental Risk Assessment has not been carried out, since it is not expected that the approval of the product will lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.5 Discussion on the non-clinical aspects

Pharmacological, pharmacokinetic and toxicological characteristics of paracetamol as presented in the non-clinical overview are based on literature review and the non-clinical overview is considered appropriate. The non-clinical overview has addressed the pharmacological and toxicological literature as well as some product-specific consideration. There are no issues relating to the pharmacology or toxicology and formulation of paracetamol. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Paracetamol is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this application, the MAH has requested a biowaiver, which is discussed below.

IV.2 Pharmacokinetics

Paracetamol is readily absorbed from the gastrointestinal tract with peak plasma concentration occurring about 30 minutes to two hours after oral administration. Paracetamol is distributed rapidly throughout all tissues. At therapeutic doses protein binding is negligible.

In adults, paracetamol is conjugated in the liver with glucuronic acid (~60%), sulphate (~35%) conjugates. The latter route is rapidly saturated at doses higher than the therapeutic dose. A minor route, catalysed by the cytochrome P450, results in the formation of an intermediate reagent (NAPQI) which under normal conditions of use is rapidly detoxified by glutathione and eliminated in the urine, after conjugation with cysteine (~3%) and mercaptopuric acid.

In neonates and children <12 years sulphate conjugation is the main elimination route and glucuronidation is lower than in adults. Total elimination in children is comparable to that in adults, due to an increased capacity for sulphate conjugation.

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

In cases of renal or hepatic insufficiency, after overdose, and in neonates the elimination half life of paracetamol is delayed. The maximum effect is equivalent with plasma concentrations. For elderly patients, the capacity for conjugation is not modified.

Biowaiver
Paracetamol is a BCS Class I drug (high permeability and high solubility) with a wide therapeutic index and a biowaiver can be accepted.

The product contains magnesium stearate which is known to affect solubility of drugs. However, magnesium stearate is an excipient which is widely present in different paracetamol formulations and the amount present in the proposed formulation is not considered to affect absorption. Other excipients not present in the reference product i.e. gelatin, croscarmellose sodium, starch are considered as inactive and not expected to influence the absorption of paracetamol from the formulations.

Dissolution of paracetamol from the product to be marketed showed very rapid to rapid dissolution. Dissolution was slower than the products on the Dutch and Belgium market. The slower is likely caused by the use of gelatin as ingredient in the MAH products.

In the provided literature a wide variety of formulations are used. Considering the fact that paracetamol is a BCS Class I drug, the product does not contain excipients which may affect the systemic exposure of paracetamol and the very rapid to rapid dissolution of paracetamol over the pH range of 1.2 - 6.8, a comparable exposure is expected with regard to the formulations used in literature.

IV.3 Pharmacodynamics

Despite paracetamol is well established, its mode of action underlying its analgesic and antipyretic effect is not fully understood. Paracetamol is a weak inhibitor of cyclo-oxygenase-1 and -2, which are important for the prostaglandin synthesis. The lack of an anti-inflammatory effect cannot be explained by this. It is possible that the distribution of paracetamol throughout the body and thus the site where inhibition of prostaglandin synthetase takes place also plays a role. Of interest, new insights have suggested that the analgesic effect of paracetamol may also be due to the indirect activation of cannabinoid CB1 receptors (CNS Drug Reviews 2007; 12: 250–75).
In conclusion, the pharmacodynamic characteristics of paracetamol have been adequately addressed in the clinical overview and SmPC.

IV.4 Clinical efficacy

The MAH discussed several studies and systematic overviews regarding analgesic and antipyretic effects of paracetamol. The main studies are summarised in two tables that were created by the RMS (see Table 1 and Table 2 below).

Analgesic effect

In the studies provided in the overview regarding dental procedures, migraine and post-operative pain, paracetamol was superior to placebo (Table 1), e.g. 50% pain relief after one hour were 62,5% for paracetamol in comparison to 29% for placebo for patients with third molar extraction (p ≤0.05, Sunshine et. al., 1986).

Table 1: Analgesic effects

Study	Design	Endpoints	N	Age	Safety conclusions	Efficacy conclusions
Sunshine (1986)	RCT, DB, PC, parallel, single dose Paracetamol/ Placebo	Pain relief scores	182 30 30	Mean age of 22.3	Paracetamol: headache	Paracetamol was superior to placebo (5th hour: 36% for paracetamol and 32.5% for placebo).
Toms (2008)	Systematic search (Cochrane) of RCT, DB, PC Paracetamol 500/650/1000 mg/ Placebo	At least 50% pain relief over four to six hours	Patients with postoperative pain 5762 3277 2425	Adults	NA	46% (1507 of 3277) patients treated with paracetamol achieved at least 50% pain relief over four to six hours, compared to 20% (485 of 2425 patients) with placebo. There was no clear dose response relationship. About half of participants needed additional analgesia over 4-6 hrs, compared with about 70% in placebo arm.
Cooper (1981, 1983)	Systemic review of 35 RCT, DB, AC, PC studies Aspirin/ Paracetamol/ Placebo	Reduction of pain measured by pain intensity scores (0-5 with 0 no pain and 5 very severe pain).	Patients with moderate to severe pain 32 not reported 87	Adults	NA	Paracetamol and aspirin were equianalgesic Pain-relief score after 2 hours: 2.33 for Paracetamol 2 for Aspirin 0.75 for Placebo
Peters (1983)	RCT, DB, Parallel Aspirin/ Paracetamol/ Placebo	Pain intensity difference and pain Relief scores analyses.	 90 87 92	Adults	NA	Both paracetamol and aspirin are significantly more effective than placebo (2-6h). Cumulative TOPAR means: paracetamol and aspirin were twice as effective as placebo beyond one hour and 1.5 times as effective beyond 3 hours.
Dionne (1983)	RCT, DB, PC, AC Ibuprofen/ Paracetamol + codeine/ Placebo	Mean of pain intensity (2 doses, 1st prior to surgery, second after)	Patients with third molar surgery 107	Adults	NA	Paracetamol is superior to placebo, however ibuprofen was superior to paracetamol and placebo. Mean pain intensity (sum of both doses): Ibuprofen: 4.42 Paracetamol: 9.12 Placebo: 11.28
Maclean (1983)	RCT, DB, crossover Paracetamol 1g 3 times a day/ Flurbiprofen 100mg 3 times a day	Mean pain relief score (0 = no relief to 4 = very good relief)	25	Young women with dysmenorrhoea	Flurbiprofen: migraine (1p) and nausea/feeling faint (1p)	Mean pain relief scores (SE) on the worst day for paracetamol and flurbiprofen were 1.12 (0.42) and 4.53 (0.59), respectively (p < 0.01).
Frank	DB, AC,	Mean pain	35	Young	Flurbiprofen: gastro-	The mean pain relief scores (SE)

(1983)	crossover Paracetamol/ flurbiprofen	relief score (0-8 with 0 no pain and 8 very severe pain).		women with dysmenorrhoea	intestinal (4p) and nervous system (1p) Paracetamol: gastro-intestinal (5p) and nervous system (2p)	on the worst day: Paracetamol: 5.06 (0.57) flurbiprofen: 6.41 (0.57). (p < 0.01 for difference paracetamol vs. flurbiprofen)
Kiersch (1994)	RCT, DB, PC, single dose Naproxen sodium 440 mg/ Paracetamol 1000 mg/ Placebo	Total Pain relief score (TOTPAR, 0-4 h) 50% pain reduction Time to re-medication	Patients with post operative dental pain 92 89 45	Mean age of 23.5	Nausea, vomiting, headache Naproxen Sodium (35%) Paracetamol (29%)	Paracetamol is superior to placebo. TOTPAR at 4 h (mean): Placebo: 2.2 Naproxen: 6.9 Paracetamol: 4.7 (p = 0.002 for paracetamol vs. placebo) Time to 50% pain reduction (h): Placebo: 0.1 Naproxen: 0.4 Paracetamol: 0.2 (p=0.150 for placebo vs. paracetamol) The time to re-medication (h) Placebo: 2.0 (95% CI = 7.9-12h) Naproxen: 9.9 (95% CI = 2.1-5h h) Paracetamol: 3.1 (95% CI = 1.1- 2 h) (p = 0.063 for paracetamol vs placebo)
Cooper (1989)	RCT, DB, PC, single-dose Ibuprofen 400mg/ Paracetamol 1000mg/ Placebo	Sum Pain Intensity Difference (SPID) Total Pain Relief (TOTPAR) Sum pain half-gone	Patients with post surgical dental pain n = 184 61 59 64	Mean age of 23.1	Drowsiness Nausea Dizziness Headache Nervousness Chills Ibuprofen (83%) Paracetamol (84%)	Both active agents were superior to placebo. SPID (mean ± SEM): Ibuprofen: 5.7 ± 0.7 Paracetamol: 3.4 ± 0.7 Placebo: 0.1 ± 0.6 (P < 0.05 for ibuprofen vs. paracetamol). TOTPAR: Ibuprofen: 13.1 ± 0.7 Paracetamol: 10.2 ± 0.7 Placebo: 4.7 ± 0.6 (p < 0.05 for ibuprofen vs. paracetamol). Sum pain 50% reduction: Ibuprofen: 3.4 ± 0.3 Paracetamol: 2.5 ± 0.3 Placebo: 1.2 ± 0.2 (p < 0.05 for ibuprofen vs. paracetamol).
Zang in **Nikles** (2005)	Meta-analysis of 10 RCT, DB, PC studies Paracetamol/ NSAID/ Placebo	Pain reduction from baseline	Patients with osteoarthritis n = 1712	Adults	GI discomfort: (RR for NSAIDs vs. Paracetamol was 1.35 (95% CI 1.05 - 1.75))	Paracetamol is an effective agent for pain relief in patients with osteoarthritis. Although better tolerated, it is less effective than NSAIDs. Effect size (95% CI): Paracetamol vs. placebo: 0.21 (0.02 to 0.4) NSAIDs vs. paracetamol: 0.20 (0.10 to 0.30)

Antipyretic effect

In both adults and children is paracetamol superior to placebo in fever reduction. Significant more children became afebrile at short notice with paracetamol in comparison to placebo (45% vs. 10%) (Autret, 1994; Table 2). Additionally, both paracetamol and ibuprofen are equivalent in terms of temperature reduction (degrees and percentage) and duration of reduction in temperature in the first four hours of treatment (Amdekar, 1985).

Table 2: Antipyretic effects

Study	Design	Endpoints	N	Age	Side-effects	Outcome
Kauffman (1992)	RCT, DB, PC, double-dummy Ibuprofen 10mg/kg; Ibuprofen 7.5mg/kg; Paracetamol 10mg/kg; Placebo	Area under the curve (AUC) for % change in temperature	Children with acute febrile illness 38 8 12 8 9	2 to 12 years	-	All three active treatments produced significant antipyretic effect compared with Placebo AUC of percentage change in temperature (95% CI): Ibuprofen 10mg/kg: 590 (160-875) Ibuprofen 7.5mg/kg: 730 (576-839) Paracetamol: 328 (-356-686) Placebo: -67 (-629-120) Ibuprofen provided greater temperature decrement and longer duration of antipyretic effect than paracetamol (reduction of 1ºC for paracetamol vs. 1.8ºC for Ibuprofen 7.50mg/kg).
Walson (1992)	RCT, DB, AC, parallel group, multi-dose, variable-duration 2.5-, 5-, or 10mg/kg ibuprofen 15-mg/kg; paracetamol every 6 hours for 24 to 48 hours	Reduction of fever measured by temperature changes	Febrile children (defined as oral or rectal temperature of 39°C to 40.5°C) 64 15 per group 16	6 months-11 years	141 mild adverse effects reported. Ibuprofen: 124/141 Paracetamol: 48/141 4 patients withdrawn: 1 with complaints of moderate nausea, vomiting, and abdominal pain (Ibuprofen) 3 patients had hypothermia occurring after administration of two to three doses (paracetamol).	There were no significant differences in temperature response between the two treatment groups of ibuprofen 10mg/kg and paracetamol 15mg/kg after the second dose. Both groups were more effective than lower doses of ibuprofen (2.5 and 5 mg/kg) Mean percentage of change from baseline (%): Ibuprofen 2.5mg/kg: 34.5 Ibuprofen 5mg/kg: 38.9 Ibuprofen 10mg/kg: 73.2 Paracetamol 15mg/kg: 65.9
Autret (1994)	RCT, DB, parallel group Ibuprofen 7.5mg/kg (syrup) Paracetamol 10 mg/kg (syrup)	AUC for reduction in temperature (%)	Children with fever (≥38ºC) associated with infectious diseases and treated with antibiotic therapy. n = 154 77 77	6 months – 5 years	Ibuprofen: gastrointestinal symptoms (5/9), skin reactions (3/9) epistaxis (1/9) Paracetamol: gastrointestinal symptoms (2/5), Skin reactions (2/5), epistaxis (1/5)	Temperature change over time was not significantly different between the two groups. The temperature reduction over the first 4 h of treatment was significantly higher after ibuprofen (60%) than paracetamol (45%). Both ibuprofen and paracetamol were well tolerated.

Overall, the provided literature is considered sufficient to support that paracetamol is well established in the treatment of mild to moderate pain and fever in both adults and children.

IV.5 Clinical safety

In general, paracetamol is well tolerated at therapeutic dose levels. In contrast to NSAID, gastric intolerability and bleeding disorders do practically not occur at regular use of paracetamol. Asthmatic reactions may occur in patients with a history of asthma, but significantly less than NSAIDs. Rare cases of nephropathy and severe dermal reactions including Steven-Johnsons syndrome, toxic epidermal necrolysis, and acute generalised exanthematous pustulosis have been reported. In 2014, the PRAC concluded that causality is yet unclear of severe skin reactions, but that a warning in the SmPC section 4.8 that "Very rare cases of serious skin reactions have been reported" would be appropriate.

The main clinical risk of high doses of paracetamol is liver failure, due to the hepatotoxic effects of the paracetamol metabolite NAPQI. The toxic paracetamol metabolite NAPQI can normally be inactivated in the liver by conjugation with glutathione. When high amounts of paracetamol are ingested, the normal glutathione amount in liver cells is not sufficient to inactivate all formed NAPQI, resulting in hepatotoxicity. Patients with renal or hepatic impairment, and patients using other hepatotoxic substances like alcohol, should be recommended to use lower dose. This has been adequately addressed in the SmPC.

If hepatotoxicity occurs, the most efficacious way to prevent paracetamol-induced hepatotoxicity is the timely administration of the antidote N-acetylcysteine (NAC). NAC, an acetylated cysteine residue, is a precursor of glutathione, and NAC administration results in increased hepatic glutathione concentrations. NAC therapy has been associated with anaphylactoid symptoms such as rash, flushing, pruritus and angioedema and hypotension, nausea and vomiting, and pulmonary symptoms such as shortness of breath and bronchospasm, and chest pain.

In conclusion, the safety overview by the MAH is considered adequate. At normal use, paracetamol is well-tolerated. Adequate warnings and dose recommendation have been included in the SmPC for patients at risk.

IV.6 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 Kruidvat Paracetamol 500 mg tablets.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	• Hepatotoxicity/ abnormal liver function (Patients with pre-existing liver disease, chronic alcoholism, malnutrition, dehydration, underweight adults) • Overdose (non-intentional and intentional)

	• Interaction with anticoagulants • Interaction with enzyme inducers
Important potential risks	• Medication overuse headache
Missing information	• Use by children <6 years of age (500 mg tablets)). • Medication errors

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.7 Discussion on the clinical aspects

Paracetamol 500 mg is considered widely established. Paracetamol is an effective antipyretic drug. Though its analgesic capacity may be modest as compared to NSAIDs, and its efficacy in certain pain models such as low back pain is debated, paracetamol may serve as a better tolerated alternative for NSAIDs. Moreover, systematic reviews on post-operative pain indicate that paracetamol can provide a clinically relevant effect. In contrast to NSAIDs, it lacks anticoagulant and gastro-intestinal side effects, and it can be safely used in e.g. post-operative setting, and cardiovascular patients, elderly and patients with a history of gastro-intestinal ulcera.
No bioequivalence studies were performed. This is accepted. Paracetamol is a BCS Class I drug (high permeability and high solubility) with a wide therapeutic index. The dissolution data at a pH 1.2, 4.5 and 6.8 between test and formulation used in literature (more than 85% within 15 min.) demonstrated similarity. No interference with absorption is expected from the excipients of this product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Kruidvat Paracetamol liquid caps 500 mg, soft capsules (NL Licence RVG 116359). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Kruidvat Paracetamol has a proven chemical-pharmaceutical quality. Kruidvat Paracetamol 500 mg is an effective analgesic and antipyretic drug, which is considered widely established. The benefit/risk balance is considered positive.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Kruidvat Paracetamol 500 mg, tablets with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finalised with a positive outcome on 24 April 2018.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse