COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Paracetamol Apotex 1000 mg, tablets

(paracetamol)

NL License RVG: 118955

Date: 14 October 2020

This module reflects the scientific discussion for the approval of Paracetamol Apotex 1000 mg, tablets. The procedure was finalised on 2 August 2019. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
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
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 Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Paracetamol Apotex 1000 mg, tablets, from Apotex Europe BV.

The product is indicated for:

- Fever and pain with flu and cold;
- Fever and pain after vaccination;
- Headache;
- Toothache;
- Nerve pain;
- Lumbago;
- Muscle strain;
- Menstrual pain.

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

This national procedure concerns a bibliographical application based on well-established medicinal use of tablets containing the active substance paracetamol. This type of application does not require submission of the results of pre-clinical tests or clinical trials if the Marketing Authorisation Holder (MAH) can demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety. "Medicinal use" does not exclusively mean "use as an authorised medicinal product'', so that the proof of medicinal use may be submitted even in the absence of a marketing authorisation. Well-established use refers to the use for a specific therapeutic use. For this kind of application, a detailed description of the strategy used for the search of published literature and the justification for inclusion of the references in the application has to be provided. The documentation submitted by the MAH should cover all aspects of the efficacy and/or safety assessment and must include a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies.

In addition, this national procedure concerns a line extension to the registered product Paracetamol Apotex 500 mg, tablets which has been registered in The Netherlands by the same MAH (Apotex Europe BV) since 29 January 1992 through a national procedure. The differences with the original product are related to the new strength.

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

II. QUALITY ASPECTS

II.1 Introduction

Paracetamol Apotex are capsule shaped, white to off-white tablets with a score line and the inscription “PARA 1000” on both sides. The tablets contain 1000 mg paracetamol and can be divided into two equal doses.

The tablets are packed in PVC/Alu blisters or polypropylene bottles with a PE lid and a PE filler that also forms the separation between tablets and package leaflet in the bottle.

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 sparingly soluble in water. The molecule does not contain a chiral centre and only one grade of polymorphic form.

The CEP procedure is used for 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 European Pharmacopoeia.

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

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the Ph. Eur. and CEPs with an additional test for acetic acid. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance
The active substance is stable for 4 years when stored under the stated conditions. Assessment thereof was part of granting the CEP 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. The formulation is based on the paracetamol 500 mg tablets. Adequate information has been provided regarding the dissolution profiles at pH 1.0, 4.5 and 6.8, justifying the similarity between the 500 mg and the 1000 mg tablets. Overall, the pharmaceutical development is acceptable.

Manufacturing process

The tablets are manufactured by a wet granulation technique, which is common for this type of dosage form. The manufacturing process has been validated according to relevant European guidelines. A post-approval process validation scheme for the complete manufacturing process of the first three full scale commercial bathes is provided.

Control of excipients

The excipients comply with Ph. Eur. These specifications are acceptable. 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, uniformity of dosage units, uniformity of mass of tablet halves, disintegration, hardness, microbial quality, identification, content, dissolution, residual moisture and related substances. The release and shelf-life limits are identical, except for hardness and residual moisture. 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 two full-scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for two full-scaled batches stored at 25°C/60% RH (36 months), 30°/65% RH (36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. On basis of the data submitted, a shelf life was granted of three years. The labelled storage condition 'This medicinal product does not require any special storage conditions' is justified. Stability data have been provided demonstrating that the product remains stable for 6 months following first opening of the flacon.

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

A Certificate of suitability issued by the EDQM for gelatin is provided and considered acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Paracetamol Apotex 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 Ecotoxicity/environmental risk assessment (ERA)

The product is intended as a substitute for other paracetamol products on the market. The approval of this product will not result in an increase in the total quantity of paracetamol released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

III.2 Discussion on the non-clinical aspects

For the non-clinical studies with paracetamol, reference is made to the existing marketing authorisation of Paracetamol Apotex 500 mg tablets. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the MEB agrees that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Pharmacology and pharmacodynamics

The main action of paracetamol is the inhibition of cyclo-oxygenase, an enzyme which is important for the prostaglandin's synthesis. Central nervous system cyclo-oxygenase is more sensitive for paracetamol than peripheral cyclo-oxygenase and this explains why paracetamol has an antipyretic and analgesic efficacy, without a conspicuous peripheral anti-inflammatory activity (Flower et al 1985, Meredith et al 1980, Clissold 1986, Ferreira et al 1978).
Paracetamol has only weak anti-inflammatory effects and has been thought to have a generally poor ability to inhibit COX in the presence of high concentrations of peroxides, as are found at sites of inflammation. However, this aspect of its action has not been addressed rigorously. Certainly, the most commonly consumed daily dose, 1000 mg, results in roughly 50% inhibition of both COX-1 and COX-2 in whole blood assays *ex vivo* in healthy volunteers. It has been suggested that COX inhibition might be disproportionately pronounced in the

brain, explaining its antipyretic efficacy (Boutaud et al 2002, Ouellet et al 2001, Catella-Lawson et al 2001 in Goodman 2006).
Single or repeated therapeutic doses of paracetamol have no effect on the cardiovascular and respiratory systems, on platelets, or on coagulation. Acid-base changes and uricosuric effects do not occur, nor does the drug produce the gastric irritation, erosion, or bleeding that may occur after salicylate administration (Goodman 2006).
Plasma paracetamol concentrations depend on the route of administration, volume of distribution, and clearance. Despite characterisation of the time–concentration relationship, a single-point plasma concentration imparts limited information about the relationship between concentration and effect. It is the concentration in the effect compartment rather than in the plasma that relates to the effect. Although the concentration in the effect compartment may mirror the plasma concentration, this effect compartment concentration is subjected to time delays, and the maximum effect compartment concentration is less than the maximum plasma concentration after a single dose. The time delays are dependent on body size, being shorter with decreasing body size, characterised by weight. Relationships between this effect compartment paracetamol concentration and analgesia and antipyresis have been described using sigmoid E_{max} models. A minimum target effect compartment concentration of 5 mg/l for fever and 10 mg/l for pain do not seem unreasonable on the basis of current literature. Some effect will be observed at lower concentrations because the response is part of a continuum, not an all-or-nothing phenomenon (Gibb et al 2008).

Although paracetamol is well-established in the treatment of mild to moderate pain and fever, 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. Central nervous system cyclo-oxygenase is more sensitive for paracetamol than peripheral cyclo-oxygenase and this may explain why paracetamol has an antipyretic and analgesic effect without a conspicuous peripheral anti-inflammatory activity. In conclusion, the exact mechanism of action of paracetamol is not fully understood, though it has been established that paracetamol act as an COX-1 and COX-2 inhibitor.

IV.2 Pharmacokinetics

Biowaiver
In order to show similar dissolution profiles between Paracetamol Apotex 1000 mg tablets with the currently registered Paracetamol Apotex 500 mg tablets, the MAH has performed *in vitro* dissolution studies in pH 1.0, 4.5 and 6.8.
According to the Guideline on the Investigation of Bioequivalence, the following criteria must be met where a waiver for additional strength(s) is claimed:

a. the products are manufactured by the same manufacturing process
b. the qualitative composition of the different strengths is the same
c. the composition is quantitatively proportional
d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

Paracetamol is not considered to be a Narrow Therapeutic Index drug. It is agreed with the MAH that nowadays it is accepted that paracetamol, in a conventional immediate release formulation, does not give rise to bioavailability problems and can be considered to be a class I drug, which would allow a biowaiver in which case similarity of dissolution profiles has to be demonstrated.
Paracetamol Apotex 1000 mg tablets (and Paracetamol 500 mg tablets) have shown rapid (85% within 30 min) *in vitro* dissolution characteristics. The excipients used in the composition of the test medicinal product (maize starch, gelatine, croscarmellose sodium, magnesium stearate and purified water) are well established and employed in usual amounts. No interactions affecting drug bioavailability and/or solubility characteristics are known from these excipients. Both strengths are quantitatively dose proportional.

Therefore, the requested biowaiver for this product can be granted.

IV.3 Clinical efficacy

Therapeutic effect
Paracetamol has been used extensively for the relief of mild to moderate pain. It is effective in both acute and chronic conditions such as headache, migraine, dysmenorrhea, sore throat, musculoskeletal pain, soft-tissue injury, pain after vaccination, and pain after dental procedures/tooth extraction, toothache, and the pain of osteoarthritis (Nikles et al 2005). Paracetamol is widely used as a supplement to or in combination with opioid analgesia in the management of more severe pain states (such as cancer pain) as well as being an accepted treatment of the relief of fever. The efficacy of paracetamol in acute and postoperative pain has been established in many clinical trials, with single doses of 600-1000 mg showing greater activity than placebo (Moore et al 1997, 2003 in Nikles et al 2005).
Paracetamol is particularly indicated in cases of aspirin allergy, haemostatic disturbances (including anticoagulant therapy, bleeding diatheses (e.g. haemophilia), upper gastrointestinal disease (e.g. ulcer, gastritis, hiatus hernia) and gouty arthritis, a variety of arthritic and rheumatic conditions involving musculoskeletal pain. As analgesic and antipyretic it is used in case of discomfort and fever caused by influenza and common cold and after vaccination (Drug Facts and Comparisons 1988, USP-DI 2007, Flower et al 1985, Offerhaus 1986, Clissold 1986). Alcoholics and patients with alcoholic liver cirrhosis should not use paracetamol. This combination is known as "therapeutic misadventure" (Offerhaus 1986).

Paracetamol compared with placebo
In several studies paracetamol and paracetamol in combination with codeine were compared with placebo. Cooper (1981,1983) conducted more than 35 different studies in oral surgery pain, comparing many oral analgesic agents. Well-designed studies have included a placebo comparison and paracetamol has generally proved to be a superior analgesic compared to placebo.
In a study by Peters et al (1983) aspirin (650 mg) and paracetamol (1000 mg) were compared with each other and with placebo in patients (N=307) with moderately severe headache. Both aspirin and paracetamol were significantly more effective than placebo.

In a postoperative pain study by Dionne et al (1983) in dental outpatients (N=107), the combination of paracetamol 600 mg plus codeine was distinguishable from placebo but not from paracetamol 600 mg alone.
Weil et al (2007) conducted a systematic review to assess the beneficial and harmful effects of paracetamol for pain relief after surgical removal of lower wisdom teeth, compared to placebo, at different doses and administered postoperatively. Randomised, parallel group, placebo controlled, double blind clinical trials of paracetamol for acute pain, following third molar surgery were selected. The proportion of patients with at least 50% pain relief was calculated for both paracetamol and placebo. The number of patients experiencing adverse events, and/or the total number of adverse events reported were analysed.
Twenty-one trials met the inclusion criteria. A total of 2048 patients were initially enrolled in the trials (1148 received paracetamol, and 892 the placebo) and of these 1968 (96%) were included in the meta-analysis (1133 received paracetamol, and 835 the placebo). Paracetamol provided a statistically significant benefit when compared with placebo for pain relief and pain intensity at both 4 and 6 hours. Most studies were found to have moderate risk of bias, with poorly reported allocation concealment being the main problem. Risk ratio values for pain relief at 4 hours 2.85 (95% confidence interval (CI) 1.89 to 4.29), and at 6 hours 3.32 (95% CI 1.88 to 5.87). A statistically significant benefit was also found between up to 1000 mg and 1000 mg doses, the higher the dose giving greater benefit for each measure at both time points. There was no statistically significant difference between the number of patients who reported adverse events, overall this being 19% in the paracetamol group and 16% in the placebo group. Paracetamol is a safe, effective drug for the treatment of postoperative pain following the surgical removal of lower wisdom teeth.

Toms et al (2008) assessed the efficacy of single dose oral paracetamol for the treatment of acute postoperative pain and searched The Cochrane Library, MEDLINE, EMBASE, the Oxford Pain Relief Database and reference lists of articles to update an existing version of the review in July 2008. The existing version was from 2004 [Barden et al (2004) in Toms et al (2008). Randomised, double-blind, placebo-controlled clinical trials of paracetamol for acute postoperative pain in adults were included.
Area under the “pain relief versus time” curve was used to derive the proportion of participants with paracetamol or placebo experiencing at least 50% pain relief over four to six hours, using validated equations. Number-needed-to-treat-to-benefit (NNT) was calculated, with 95% confidence intervals (CI). The proportion of participants using rescue analgesia over a specified time period, and time to use, were sought as measures of duration of analgesia. Information on adverse events and withdrawals was also collected.
Fifty-one studies, with 5762 participants, were included: 3277 participants were treated with a single oral dose of paracetamol and 2425 with placebo. About half of participants treated with paracetamol at standard doses achieved at least 50% pain relief over four to six hours, compared with about 20% treated with placebo. NNTs for at least 50% pain relief over four to six hours following a single dose of paracetamol were as follows: 500 mg NNT 3.5 (2.7 to 4.8); 600 to 650 mg NNT 4.6 (3.9 to 5.5); 975 to 1000 mg NNT 3.6 (3.4 to 4.0). There was no dose response. Sensitivity analysis showed no significant effect of trial size or quality on this outcome.
About half of participants needed additional analgesia over four to six hours, compared with about 70% with placebo. Five people would need to be treated with 1000 mg paracetamol,

the most commonly used dose, to prevent one needing rescue medication over four to six hours, who would have needed it with placebo. Adverse event reporting was inconsistent and often incomplete. Reported adverse events were mainly mild and transient, and occurred at similar rates with 1000 mg paracetamol and placebo. No serious adverse events were reported. Withdrawals due to adverse events were uncommon and occurred in both paracetamol and placebo treatment arms. It was concluded by Toms et al (2008) that a single dose of paracetamol provides effective analgesia for about half of patients with acute postoperative pain, for a period of about four hours, and is associated with few, mainly mild, adverse events.

The aim of a study by Renner et al (2007) was to determine the analgesic effect of acetaminophen compared to a combination of both caffeine and acetaminophen or caffeine alone using tonic and phasic pain stimulation. Twenty-four subjects were treated orally with 1000 mg acetaminophen, 130 mg caffeine, and a combination of both in a 4-way crossover, double-blind, placebo-controlled study. Pharmacokinetics and analgesic effects were assessed by means of an experimental pain model based on pain-related cortical potentials after phasic stimulation of the nasal mucosa with CO2 and based on pain ratings after tonic stimulation with dry air. Analgesic effects of acetaminophen and acetaminophen plus caffeine but not caffeine alone caused a significant reduction of pain-related cortical potentials beginning 30 minutes after medication.
The combination demonstrated an enhanced effect throughout the observation time up to 3 hours. Caffeine accelerated acetaminophen absorption, indicated by enhanced early AUCs. Significant analgesic effects of the combination on tonic pain ratings were found throughout the observation time as compared to acetaminophen and placebo. In this study, caffeine enhanced and prolonged the analgesic activity of acetaminophen.

<u>Paracetamol compared with NSAIDs</u>
Many studies have evaluated the analgesic efficacy of paracetamol in comparison with different NSAIDs (Cooper 1983, Dionne et al 1983, Frank et al 1983, Maclean 1983, Olstad et al 1986, Sunshine et al 1986). The results demonstrated that non-steroidal drugs such as ibuprofen, diflunisal, flurbiprofen, naproxen, and zomepirac sodium produced significantly greater analgesia than paracetamol and aspirin.

Mild to moderate acute pain
In two double-blind crossover studies by Maclean (1983) and Frank et al (1983) flurbiprofen was compared with paracetamol (3x1000mg per day) in the treatment of primary dysmenorrhoea. Flurbiprofen was statistically significantly better in treatment of pain and the majority of the patients preferred flurbiprofen over paracetamol.

Moderate to severe acute pain
In a randomised, double-blind study by Bondarsky et al (2013), patients received either ibuprofen 800 mg, paracetamol1000 mg or their combination. 30 patients were included in each treatment group. Pain decreased over the one hour study period for all groups ($p < .001$) with mean (SD) scores about 20 mm lower on the Visual Analogue Scale than the mean initial score. However, there was no significant difference among treatments ($p = .59$). The need for rescue analgesics was similar across groups.

In a placebo controlled double-blind randomised study by Sunshine et al (1986) paracetamol alone (650 mg) , paracetamol (650 mg) in combination with codeine (60 mg), flurbiprofen (50 mg and 100 mg), and zomepirac sodium (110 mg) were compared for relative analgesic efficacy after extraction of the third molar. The results showed that there is a clear separation between active treatments and placebo, with zomepirac having greatest efficacy, followed by flurbiprofen at both doses, the combination of paracetamol and codeine, and, finally, paracetamol alone.

Kiersch et al (1994) compared the analgesic efficacy and duration of action of naproxen sodium 440 mg (n = 92), paracetamol 1000 mg (n=89), and placebo (n=45) in a single-dose, randomised, double-blind, 12-hour study of patients with at least moderate pain secondary to extraction of three of four third molars. Time to remedication, a measure of duration of analgesic effect, was significantly longer ($P<0.001$) with naproxen sodium (median, 9.9 hours) than with either paracetamol (median, 3.1 hours) or placebo (median, 2.0 hours).

Sunshine et al (1993) performed a randomised, double-blind parallel study compared the efficacy and safety of single doses of 100 mg or 50 mg ketoprofen, the combination of 650 mg paracetamol plus 10 mg oxycodone hydrochloride, 650 mg paracetamol, or placebo in 240 patients with severe postoperative pain after caesarean section. Analgesia for the first dose was assessed over an 8-hour period. Multiple doses of 100 mg or 50 mg ketoprofen and the combination at half the dose (325 mg paracetamol plus 5 mg oxycodone) were also assessed for up to 7 days. The 100 and 50 mg doses of ketoprofen and the combination were statistically superior to paracetamol and placebo for many analgesic measures.

Cooper et al (1989) conducted a single-dose, randomised, double-blind, placebo-controlled study to determine the relative analgesic efficacy of ibuprofen 400 mg and paracetamol 1000 mg, using a standard assay for analgesic agents, the dental pain model. Both active agents were effective compared to placebo. Ibuprofen 400 mg was more effective than paracetamol 1000 mg for Sum Pain Intensity Difference (SPID), Total Pain Relief (TOTPAR), sum pain half-gone, and overall evaluation ($P<0.05$ to $P<0.001$).

A randomised double-blind trial was performed to evaluate efficacy and tolerability of suprofen 200 mg (Suprocil) in comparison to paracetamol 500 mg after surgical extraction of a wisdom tooth (Reijntjes et al 1987). The 30-min pain relief with paracetamol was superior to that obtained with suprofen. Roughly, the 90-min pain relief scores were somewhat higher for suprofen than for paracetamol. However, none of the differences were statistically significant.

Forbes et al (1990) evaluated ketorolac, ibuprofen, paracetamol, and a paracetamol-codeine combination in postoperative oral surgery pain. Two-hundred six outpatients with postoperative pain after the surgical removal of impacted third molars were randomly assigned on a double-blind basis to receive oral doses of ketorolac tromethamine 10 and 20mg, ibuprofen 400 mg, paracetamol 600 mg, a combination of paracetamol 600 mg plus codeine 60 mg, or placebo. Using a self-rating record, subjects rated their pain and its relief hourly for 6 hours after medicating. All active medications were significantly superior to placebo. Analgesia was similar for ketorolac 10 and 20 mg and ibuprofen 400 mg; however, these treatments were superior to paracetamol alone and the paracetamol-codeine combination.

The efficacy of naproxen and paracetamol in relieving uterine cramps has been compared in a sequential trial (Skovlund et al 1991). The treatments did not differ significantly in a two-sided test in 56 patients.

Chronic mild to moderate pain
A Cochrane review has been conducted to assess paracetamol's role in chronic pain associated with osteoarthritis. Towheed et al (2003, in Nikles et al 2005) found that it was less effective overall than NSAIDs in terms of focal pain reduction and global pain assessments, although the effect sizes for these differences were modest at 0.2 to 0.5. The relative superiority of NSAIDs over paracetamol appears to be more marked in osteoarthritis patients with more severe pain.
Zhang et al (2004 in Nikles et al 2005) conducted a meta-analysis of available evidence (to July 2003) to reassess the rationale for using paracetamol in the treatment of osteoarthritis. As with the Cochrane review, this analysis found that paracetamol does provide effective pain relief, although it is less effective than NSAIDs. Nonetheless, based on its superior safety profile, these authors recommend that paracetamol be used as first-line treatment and that NSAIDs be reserved for those patients who do not respond.
Davies et al (2008) conducted a systematic review of randomised controlled trials to assess the efficacy of paracetamol in the treatment of pain and disability in patients with non-specific low back pain. Out of 205 unique articles found in the searches, 7 eligible trials were identified. The trials enrolled a total of 676 participants with 5 investigating acute low back pain, 1 investigating chronic low back pain and 1 investigating both. No trial provided data comparing paracetamol to placebo and only one trial compared paracetamol to no treatment. No trial reported a statistically significant difference in favour of paracetamol. There is insufficient evidence to assess the efficacy of paracetamol in patients with low back pain.

IV.4 Clinical safety

Adverse effects of paracetamol are rare and usually mild, although haematological reactions including thrombocytopenia, leukopenia, pancytopenia, neutropenia, and agranulocytosis have been reported. Rashes and other hypersensitivity reactions occur occasionally (Martindale (2014).

Acute liver failure
Although increased susceptibility was initially proposed in patients ingesting an overdose, acute liver failure at therapeutic dosages also has been asserted (Draganov et al 2000, Zimmerman et al 1995 in Dart et al 2007).

The purpose of this systematic review by Dart et al (2007) was to assess and compare the reported occurrence of acute liver failure in prospective trials in which subjects were administered a therapeutic dosage of acetaminophen with that in retrospective reports in which patients reported use of a therapeutic dosage of the drug. Subjects included in the analysis were adults who received repeated dosing of acetaminophen 4 g/day or lower for at least 24 hours. A total of 791 articles were identified, which included 30,865 subjects in prospective studies and 9337 patients in retrospective reports. The prospective studies reported no cases of fulminant hepatic injury, liver transplantation, or death due to acetaminophen. Causality relationship of acetaminophen for each retrospective case was assessed with the Naranjo adverse drug reaction probability scale. The mean ± SD Naranjo

score for all 103 retrospective cases was 3.2 ± 1.9, indicating a possible relationship between the increased aminotransferase levels and acetaminophen use.
Acetaminophen overdose is the most common cause of acute liver failure in Western countries, and its incidence seems to be increasing. Fortunately, most patients who have acetaminophen overdose recover with early N-acetylcysteine (NAC) therapy and supportive care, but regulatory actions are needed to prevent future cases (Fontana 2008).

Nephrotoxicity
Acetaminophen-induced nephropathy occasionally occurs in patients with acetaminophen ingestion, though is not as well characterized as hepatoxicity (Mazer et al 2008). The mechanisms of necrosis in both organs are similar, yet there are some subtle differences that remain unclear. Patients may present with isolated renal toxicity or in the setting of multisystem organ failure. The clinical course is generally one of recovery, but haemodialysis may be required as a temporising measure.

Overdose
The acute effects of overdose are gastrointestinal upset (diarrhoea, loss of appetite, nausea or vomiting, stomach cramps or pain) and increased sweating. The chronic effect of overdose is hepatotoxicity (pain, tenderness, and/or swelling in upper abdominal area) and may occur 2 to 4 days after the overdose is ingested.
The first indications of overdose may be signs and symptoms of possible liver damage and abnormalities in liver function tests, which may not occur until 2 to 4 days after ingestion of the overdose. Maximal changes in liver function tests usually occur 3 to 5 days after ingestion of the overdose. Overt hepatic disease or failure may occur 4 to 6 days after ingestion of the overdose. Hepatic encephalopathy (with mental changes, confusion, agitation, or stupor), convulsions, respiratory depression, coma, cerebral oedema, coagulation defects, gastrointestinal bleeding, disseminated intravascular coagulation, hypoglycaemia, metabolic acidosis, cardiac arrhythmias, and cardiovascular collapse may occur (USP DI 2007).

Renal tubular necrosis leading to renal failure (signs may include bloody or cloudy urine and sudden decrease in amount of urine) has also been reported in paracetamol overdose, usually, but not exclusively, in conjunction with paracetamol-induced hepatotoxicity (USP DI 2007).

Treatment of overdose
To decrease absorption - This may include emptying the stomach via induction of emesis or gastric lavage.
To enhance elimination - Instituting haemodialysis or hemoperfusion to remove paracetamol from the circulation may be beneficial if acetylcysteine administration cannot be instituted within 24 hours following ingestion of a massive paracetamol overdose. However, the efficacy of such treatment in preventing paracetamol-induced hepatotoxicity is not known.
Specific treatment - Use of acetylcysteine. It is recommended that acetylcysteine administration be instituted as soon as possible after ingestion of an overdose has been reported, without waiting for the results of plasma paracetamol determinations or other laboratory tests. Acetylcysteine is most effective if treatment is started within 10 to 12 hours

after ingestion of the overdose; however it may be of some benefit if treatment is started within 24 hours.
Monitoring - This may include determining plasma paracetamol concentration at least 4 hours following the ingestion of the overdose. Performing liver function tests (serum aspartate aminotransferase, serum alanine aminotransferase, prothrombin time, and bilirubin) at 24-hour intervals for at least 96 hours post-ingestion if the plasma paracetamol concentration indicates potential hepatotoxicity. Monitoring renal and cardiac function and administering appropriate therapy as required.
Supportive care - This may include maintaining fluid and electrolyte balance, correcting hypoglycaemia, and administering vitamin K and fresh frozen plasma or clotting factor concentrate.

Warnings
Paracetamol should be given with care to patients with impaired kidney or liver function; the British National Formulary recommends that large doses should be avoided in patients with hepatic impairment. It should also be given with care to patients with alcohol dependence, chronic malnutrition, or dehydration (Martindale 2014).

Interactions
The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic drugs or drugs that induce liver microsomal enzymes. The absorption of paracetamol may be accelerated by drugs such as metoclopramide. Excretion may be affected and plasma concentrations altered when given with probenecid. Colestyramine reduces the absorption of paracetamol if given within 1 hour of paracetamol (Martindale 2014).

As noted by the MAH, 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. Rare cases of nephropathy and severe dermal reactions including Steven-Johnsons syndrome, toxic epidermal necrolysis, and acute generalised exanthematous pustulosis have been reported.
The main clinical risk of high doses of paracetamol is liver failure. Patients with renal or hepatic impairment should be recommended to use lower dose. This has been addressed in the SmPC. 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.5 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 Apotex.

- 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. • Off-label use (chronic use)
Missing information	• Use in children <15 years of age (1000mg tablets).

The MEB agrees that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.6 Discussion on the clinical aspects

Well-established medicinal use of paracetamol within the European Community for at least ten years, with recognised efficacy and an acceptable level of safety in the proposed indication has been already established in the previous application for the 500 mg strength. The provided literature supports the efficacy of 1000 mg strength in the claimed indication, and the provided safety overview is sufficient. Moreover, the applied product strength fits in the dosing scheme.
The 1000 mg tablet is made using the same excipients and using the same manufacturing method and apparatus and is manufactured in the same plant by the same manufacturer as the 500 mg tablets. The formula of the 1000 mg tablets is, percentual, identical to that of the 500 mg tablet. In addition, paracetamol is considered BCS class I substance, and the dissolution testing provided by the MAH confirmed similarly rapid dissolution (>85% in 30 min) for both strengths. Therefore no differences in *in vivo* performance are expected between the strengths. The overall Benefit/Risk of Paracetamol Apotex 1000 mg is positive.

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, zachte capsules (RVG 116359 nationale procedure). The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Paracetamol Apotex 1000 mg, tablets has a proven chemical-pharmaceutical quality and is a legitimate line extension to Paracetamol Apotex 500 mg, tablets. Paracetamol Apotex is a well-known medicinal product with an established favourable efficacy and safety profile.

In the Board meeting of 5 July 2018, the legal status of supply of the product was discussed. A requested PDO (pharmacy and drugstore only) legal status of supply was not approved by the Board. After changing the status to PH (pharmacy only) the issue was considered resolved.

The MEB, on the basis of the data submitted, considered that efficacy and safety has been shown, and has therefore granted a marketing authorisation. Paracetamol Apotex was authorised in the Netherlands on 2 August 2019.

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

REFERENCES

Bondarsky EE, Domingo AT, Matuza NM, Taylor MB, Thode HC Jr, Singer AJ (2013) Ibuprofen vs acetaminophen vs their combination in the relief of musculoskeletal pain in the ED: a randomized, controlled trial. Am J Emerg Med 31, 1357-1360lp

Clissold SP (1986) Paracetamol and phenacetin. Drugs 32, 46-59

Cooper SA (1981) Comparative analgesic efficacies of aspirin and acetaminophen. Arch Int Med 141, 282-285.

Cooper SA (1983) New peripherally-acting oral analgesic agents. Ann Rev Pharmacol Toxicol 23, 617-647

Cooper SA, Schachtel BP, Goldman E, Gelb S, Cohn P (1989) Ibuprofen and acetaminophen in the relief of acute pain: A randomized, double-blind, placebo-controlled study. J Clin Pharmacol 29, 1026-1030.

Dart RC, Bailey E (2007) Does therapeutic use of acetaminophen cause acute liver failure? Pharmacotherapy 27, 1219-1230

Dionne RA, Campbell RA, Cooper SA, Hall DL, Buckingham B (1983) Suppression of postoperative pain by preoperative administration of ibuprofen in comparison to placebo, acetaminophen, and acetaminophen plus codeine. J Clin Pharmacol 23, 37-43

Drug facts and comparisons (1988) Kastrup EK, Olin BR, Connell SI, Schwach GH, Covington TR, DiPalma JR, Hussar DA, Lasagna L, Tatro DS, Whitsett TL Paracetamol, pages 903-908. Lippincott, Philadelphia

Ferreira SH, Lorenzetti BB, Corrêa FMA (1978) Central and peripheral antialgesic action of aspirin-like drugs. Eur J Pharmacol 53, 39-48

Ferreira SH, Lorenzetti BB, Corrêa FMA (1978) Central and peripheral antialgesic action of aspirin-like drugs. Eur J Pharmacol 53, 39-48

Forbes JA, Kehm CJ, Grodin CD, Beaver WT (1990) Evaluation of ketorolac, ibuprofen, acetaminophen, and an acetaminophen-codeine combination in postoperative oral surgery pain. Pharmacotherapy 10, 94S-105S

Frank GJ, Kefford RH (1983). Report of a double blind crossover study to compare flurbiprofen with Paracetamol in the treatment of primary dysmenorrhoea. J Int Med Res 11, suppl 2, 6-10.

Gibb IA, Anderson BJ (2008) Paracetamol (acetaminophen) pharmacodynamics: interpreting the plasma concentration. Arch Dis Child Mar 93, 241-247

Goodman & Gilman's (2006) The pharmacological basis of therapeutics, 11th edition Chapter 26, Analgesic-antipyretic agents; pharmacotherapy of gout. Para-aminophenol derivatives: acetaminophen pp 693-695. Pergamon Press, New York

Goodman & Gilman's (2006) The pharmacological basis of therapeutics, 11th edition Chapter 26, Analgesic-antipyretic agents; pharmacotherapy of gout. Para-aminophenol derivatives: acetaminophen pp 693-695. Pergamon Press, New York

Maclean D (1983) A comparison of Flurbiprofen and Paracetamol in the treatment of primary dysmenorrhoea. J Int Med Res 11, suppl 2, 1-5.

Martindale (2014) The Complete Drug Reference, 38th Edition Paracetamol pp 115-119 Pharmaceutical Press, UK-USA

Mazer M, Perrone J (2008) Acetaminophen-induced nephrotoxicity: pathophysiology, clinical manifestations, and management. J Med Toxicol 4, 2-6

Meredith TJ, Goulding R (1980) Paracetamol. Postgrad Med J 56, 459-473

Nikles CJ, Yelland M, Del Mar C, Wilkinson D (2005) The role of paracetamol in chronic pain: an evidence-based approach. Am J Ther 12, 80-91.

Offerhaus L (1986) Pijnstillers in de zelfmedicatie en de algemene praktijk. Ned Tijdschr Geneesk 130, 2332 -2334.

Olstad OA, Skjelbred P (1986) The effects of indoprofen versus paracetamol on swelling, pain and other events after surgery. Int J Clin Pharmacol Ther Tox 24, 34-38.

Peters BH, Fraim CJ, Masel BE (1983) Comparison of 650 mg Aspirin and 1000 mg Acetaminophen with each other, and with placebo in moderately severe headache. Am J Med 36-42.

Reijntjes RJ, Boering G, Wesseling H, Rijn van LJ (1987) Suprofen versus paracetamol after oral surgery. International Journal of Oral and Maxillofacial Surgery 16, 45-49

Renner B, Clarke G, Grattan T, Beisel A, Mueller C, Werner U, Kobal G, Brune K (2007) Caffeine Accelerates Absorption and Enhances the Analgesic Effect of Acetaminophen Journal of Clinical Pharmacology 47, 715-726

Skovlund E, Fyllingen G, Landre H, Nesheim BI (1991) Comparison of postpartum pain treatments using a sequential trial design: II. Naproxen versus paracetamol. Eur Journal Clin Pharm 40, 539-542

Sunshine A, Marrero I, Olson N, McCormick N, Laska EM (1986) Comparative study of flurbiprofen, zomepirac sodium, acetaminophen plus codeine and acetaminophen for the relief of postsurgical dental pain. Am J Med 80, suppl 3A, 50-54

Sunshine A, Olson NZ, Zighelboim I, De Castro A (1993) Ketoprofen, acetaminophen plus oxycodone, and acetaminophen in the relief of postoperative pain. Clin Pharmacol Ther 54, 546-555.

Toms L, McQuay HJ, Derry S, Moore RA (2008) Single dose oral paracetamol (acetaminophen) for postoperative pain in adults. Cochrane Database of Systematic Reviews 2008, Issue 4. Art. No.: CD004602.

USP-DI (2007) Acetaminophen (Systemic). USP DI® Volume I: Drug information for the healthcare professional (internet database).Thomson Micromedex. Greenwood Village, Colorado, USA.

Weil K, Hooper L, Afzal Z, Esposito M, Worthington HV, vanWijk A, Coulthard P (2007) Paracetamol for pain relief after surgical removal of lower wisdom teeth. Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD004487.