CBG MEB

Public Assessment Report

Scientific discussion

Paracetamol Accord 500 mg tablets

(Paracetamol)

NL/H/3145/001/DC

Date: 2 August 2016

This module reflects the scientific discussion for the approval of Paracetamol Accord 500 mg tablets. The procedure was finalised on 24 April 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

BCS	Biopharmaceutics Classification System
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 Member States have granted a marketing authorisation for Paracetamol Accord 500 mg tablets from Accord Healthcare Ltd.

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 application is based on article 10(a) of Directive 2001/83/EC, a so called bibliographic application based on the well-established medicinal use of paracetamol.

The concerned member states (CMS) involved in this procedure were Austria, Bulgaria, Cyprus, Estonia, Finland, France, Ireland, Latvia, Lithuania and Malta. A repeat use procedure was accepted for Denmark and Poland (NL/H/3145/001/E/001).

II. QUALITY ASPECTS

II.1 Introduction

Paracetamol Accord 500 mg is a white, uncoated capsule shaped tablet marked with “B score T” on one side and plain on the other side. The tablet can be divided into equal doses.

The tablets are packed in clear PVC-Al blisters.

The excipients used are maize starch, gelatine, silica colloidal anhydrous, talc, magnesium stearate, sodium starch glycolate (type A).

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. It has been adequately demonstrated that both manufacturers manufacture polymorphic form I, and that the polymorphic form does not change in the drug product throughout the shelf-life. A separate test in the drug substance or drug product specification is not deemed necessary.

The CEP procedure is used for both 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 European Pharmacopoeia.

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 analysis results for two batches from one manufacturer, and for three batches from the second manufacturer have been provided. The batches comply with the proposed set of specifications.

Stability of drug substance
On the basis of the CEP a re-test period of 5 years is acceptable for one manufacturer. For the other manufacturer stability data of 3 commercial scale batches have been provided. The batches were stored under both long term (25°C/60% RH for 60 months) and accelerated conditions (40°C/75% RH

for 6 months). All three batches remained stable throughout the storage period (no up- or downward trends are observed). The proposed re-test period of 5 years is therefore considered acceptable.

II.3 Medicinal Product

Pharmaceutical development
The formulation development of the product has been described, the choice of excipients is justified and their functions explained. The formulation was compared to the registered product Panadol Gladde Tablet (GlaxoSmithKline Consumer Healthcare BV, the Netherlands). *In vitro* dissolution profile of test and reference product demonstrating that the drug product release is more than 85% in 15 minutes in all four pH media and are comparable complying with BCS based biowaiver of BCS Class I drug substance according to Guideline on the Investigation of Bioequivalence. The subdivision of tablets meets the requirements of the Ph.Eur. monograph for tablets.

Manufacturing process
For the manufacturing of the tablets, the wet granulation process was selected. The product is manufactured using conventional manufacturing techniques. Process validation data on the product has been presented for five batches of commercial batch size.

Control of excipients
The excipients comply with the Ph.Eur., including appropriate limits for several functionalities related characteristics.

Quality control of drug product
The product specification includes tests for appearance, average weight, identification, uniformity of dosage units, resistance to crushing, friability, related substances, water content, assay, dissolution, subdivision of tablets and microbial contamination. The shelf-life specification is identical to the release specification. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production sites have been provided for five batches, demonstrating compliance with the release 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 (18 months) and 40°C/75% RH (6 months) and for three batches of commercial batch size stored 30°C/65% RH (up to 12 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. Photostability of the drug product was adequately demonstrated.
On the basis of the submitted data the claimed shelf-life of 30 months, without further storage condition can be granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
All the excipients used in this formulation do not have potential risk for TSE/BSE and are prepared in accordance with the relevant requirements laid down in Note for Guidance EMEA/410/01, rev3.
For gelatine a certificate of suitability issued by the EDQM has been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Paracetamol Accord 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. Overall, paracetamol is rapidly and completely absorbed, although systemic bioavailability 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 mins.

Following usual oral doses, approximately 25% of paracetamol is metabolised 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 it 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. 1 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.

The impurity profile of Paracetamol Accord 500 mg tablets was compared with that of the innovator product i.e. Panadol Gladde Tablet marketed by GlaxoSmithKline Consumer Healthcare BV and was found to be similar as no additional impurities were detected.

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 bibliographic 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 2 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, catalyzed by the cytochrome P450, results in the formation of an intermediate reagent (N-acetyl-p-benzoquinoneimine) which under normal conditions of use is rapidly detoxified by glutathione and eliminated in the urine, after conjugation with cysteine (~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
A biowaiver was applied for based on the fact that this is an article 10a well-established use application. 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 Paracetamol Accord 500 mg (test) and Panadol Gladde Tablet 500 mg (reference) demonstrated similarity (more than 85% within 15 min). Not all the excipients in the test and reference product are the same. The test 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, talc, colloidal anhydrous silica and sodium starch glycolate, are considered as inactive and not expected to cause differences in absorption of paracetamol from both formulations. A biowaiver can therefore be granted.

IV.3 Pharmacodynamics

Despite its well established use, paracetamol's 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. It has been suggested in the SmPC, that the 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. 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 exact mechanism of action of paracetamol is not fully understood, though it as been established that paracetamol act as an COX-1 and COX-2 inhibitor. The PD characteristics of paracetamol has been adequately addressed in the clinical overview and SmPC.

IV.4 Clinical efficacy

The MAH provided a comprehensive overview of several studies and systematic reviews in diverse models of mild or moderate pain, and three randomised studies on fever.

The basis for selection of these articles, however, was not clear, as the search & selection criteria were not defined in the Overview document. Data of several more severe acute pain models have been included in the Clinical Overview, that are rather treated with NSAIDs in accordance to local treatment guidelines, such as migraine, dysmenorrhoea and dental procedures, as NSAIDs are considered more effective. Note: included was a recent Australian placebo-controlled trial in 1600 subjects which indicated that paracetamol up to 4000 mg is not effective in the treatment of acute low back pain (CM Williams et al., Lancet, 27 July 2014). Low back pain is not specifically mentioned in the indication of the SmPC, which is supported.

However, as shown in the studies provided in the Overview regarding dental procedures, migraine and post-operative pain, paracetamol was superior to placebo, and although the effect size was in general modest, it could be considered clinically relevant. E.g. the treatment effect of paracetamol as

compared to placebo in systemic reviews of post-operative pain studies was about 20-30% more responders (defined as a pain reduction by 50% within 4 hrs), which is considered clinically relevant. Moreover, paracetamol also has a more favourable safety profile at therapeutic doses than NSAIDs. As shown in the overview, paracetamol has no anti-thrombotic effect and does not impair gastric mucosa in contrast to NSAIDs. Paracetamol, and not NSAIDs, are therefore widely used in post-operative setting to treat pain and fever, in addition to opioids and local anaesthesia if needed.

The MAH's overview does not mention that paracetamol is used chronically in osteoarthritis (OA). According to several treatment guidelines, paracetamol is the first-line treatment option in OA. Although the literature indicates a small effect for paracetamol in OA, its safety profile is considered favourable. As this product is intended to be marketed as an OTC product and in the SmPC it is mentioned that it is intended for short term use, it is accepted that OA was omitted from the overview.

In the studies provided, oral paracetamol was clearly superior to placebo in fever reduction, in both adults and children. Significant more children became afebrile at short notice than with placebo (46.6 vs 12.1%), indicating that the effect was clinically relevant.

The data that were provided are considered sufficient to support that paracetamol is useful and widely-established in the treatment of mild-moderate pain and fever.

IV.5 Clinical safety

As noted by the MAH in the Clinical Overview, 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 and should therefore be added.

The main clinical risk of high doses of paracetamol is liver failure, due to the hepatotoxic effects of the paracetamol metabolite N-acetyl-para-benzoquinone imine (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 a 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. N-acetylcysteine 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 (Neth J Med 2014;72(5):251-7). The intravenous infusion protocol was originally developed as a three-step loading regimen; it causes very high early peak plasma concentrations of N-acetylcysteine whereas the later maintenance infusion is associated with much lower concentrations. This pharmacokinetic profile is associated with two particular concerns: a high rate of occurrence of adverse effects that occur after the initial loading infusion, and the possibility that the maintenance phase of treatment might deliver too low a dose of N-acetylcysteine for optimum protection against liver injury. Recently described novel administration regimens offer different rates of intravenous N-acetylcysteine administration in both the loading and maintenance phases. E.g. in a randomised study by Bateman et al. in 222 patients, a short 12 hours regimen with a relatively low starting dose of 100 mg/h for the first two hours, followed by 200 mg/h in the next 10 hours, caused significantly less anaphylactoid side effects (97·5% CI 0·12–0·43), and apparently similar efficacy in terms of paracetamol intoxication treatment, compared to a conventional dosing regimen (150 mg/kg for 15 minutes, 50 mg/kg for 4 hours and 100 mg/kg for 16 hours) (Lancet 2014; 383: 697-704). Though this study was considered too small to establish non-inferiority regarding efficacy, it can be concluded that lower starting doses reduce severe side effects of N-acetylcysteine.

As the treatment recommendations of N-acetylcysteine regimens for paracetamol intoxication are moving and may differ between member states, SmPC section 4.9 states that local guidelines should be followed.

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 Paracetamol Accord 500 mg tablets.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Severe and life-threatening hypersensitivity reactions like Stevens Johnson Syndrome, toxic epidermal necrolysis and erythema multiform • 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	• Overdose leading to hepatic failure • Medication overuse headache
Missing information	• Use by children under 12 years of age • 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 reference (more than 85% within 15 min) demonstrated similarity. No interference with absorption is expected from the excipients of this product.

V. USER CONSULTATION

The package leaflet (PL) has not been evaluated via a user consultation study. Reference is made to the PL approved for Paracetamol Accord 500 mg effervescent tablets (procedure UK/H/1253/001/DC). The products are therapeutically similar products that belong to the same therapeutic class. The active ingredient of both products is paracetamol. The indications and instructions for use are identical. The

key safety messages are similar. The design and layout of the PL of Paracetamol Accord 500 mg tablets is almost identical to that approved for the PL of Paracetamol Accord 500 mg effervescent tablets and the language used in both PLs is comparable. The bridging report has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Paracetamol Accord has a proven chemical-pharmaceutical quality. Paracetamol 500 mg is an effective 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 member states, on the basis of the data submitted, considered that well-established use has been demonstrated for Paracetamol Accord, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 24 April 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Repeat-use procedure to register the product in Denmark and Poland.	NL/H/3145/ 001/E/001	E	10-9-2015	1-11-2015	Approval	Yes