IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Trebon 600 mg powder for oral solution
Acetylcysteine
PA1732/003/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

II. QUALITY ASPECTS

III. NON-CLINICAL ASPECTS

IV. CLINICAL ASPECTS

V. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

VI. REVISION DATE

VII. UPDATE

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Trebon 600 mg powder for oral solution, from Uni-Pharma Kleon Tsetis Pharmaceutical Laboratories S.A. on June 19th, 2020 for use in adults as a mucolytic therapy in chronic bronchitis and other respiratory conditions associated with thick mucus hypersecretion.

This application was submitted in June 2018 as a Decentralised Procedure in accordance with Article 10a of Directive 2001/83/EC (Well-established Use). Ireland was the RMS and the United Kingdom (Northern Ireland) was the only CMS involved in the procedure.

The applicant did not seek Scientific Advice from any Competent Authority in relation to this MAA.

Supply of Trebon is restricted subject to medical prescription, which may be renewed.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website

Name of the product	Trebon 600mg Powder for oral solution
Name(s) of the active substance(s) (INN)	Acetylcysteine
Pharmacotherapeutic classification (ATC code)	R05CB01
Pharmaceutical form and strength(s)	600mg Powder for oral solution
Marketing Authorisation Number(s) in Ireland (PA)	PA1732/003/001
Marketing Authorisation Holder	Uni-Pharma Kleon Tsetis Pharmaceutical Laboratories SA.
DCP No.	IE/H/568/001/DC
Reference Member State	IE
Concerned Member State	UK (Nothern Ireland) (XI)

II. QUALITY ASPECTS

II.1. Introduction

This application is for Trebon 600 mg powder for oral solution.

II.2 Drug substance

The active substance is Acetylcysteine, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The finished product specification is based on the pharmacopoeial monograph for the dosage form, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.7 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with EU legislation for use with foodstuffs requirements.

P.8 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical and Pharmaceutical Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Trebon 600 mg powder for oral solution.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This application for a marketing authorisation was submitted in accordance with Article 10a of Directive 2001/83/EC as amended, a well-established use application. Acetylcysteine has been in well-established use within the European Union for more than ten years, demonstrating a recognised efficacy and safety profile. A non-clinical overview has been provided, it is based on relevant published literature and written by an appropriately qualified person.

III.2 Pharmacology

No new pharmacology studies have been conducted. The applicant has submitted a summary of pharmacology of NAC based on literature sources. Much of this information relates to other potential indications for NAC and potential secondary pharmacology. NAC's mucolytic activity is reported to relate to its sulfhydryl group interacting with disulfide bonds in mucoproteins, with mucus subsequently being broken into smaller, less viscous units. There is also evidence to suggest that NAC is an expectorant via stimulatory activity on ciliary action. Many of the studies provided relate to NACs role as an antioxidant and precursor to glutathione and its use following paracetamol overdose. The pharmacological information provided though limited is considered acceptable given the well-established clinical use of this product in the proposed indication. No data relating to safety pharmacology has been submitted with the dossier. The applicant was asked to provide additional information relating to safety pharmacology data in the published literature in the day 70 LOQ. An amended overview summarising data sourced from the literature was provided, this was limited and data primarily related to toxicity rather than functional safety pharmacology measures. However, given this is a well-established use of this active clinically it is

accepted that the generation of additional non-clinical safety pharmacology data is unlikely to significantly impact the known safety profile of the product.

III.3 Pharmacokinetics

No PK studies have been conducted by the applicant. A summary of studies available in the scientific literature related to the PK of NAC in non-clinical species is provided. NAC is reportedly well absorbed following oral administration with extensive first pass metabolism resulting in relatively low bioavailability. It is widely distributed. Acetylcysteine is rapidly metabolised to cysteine and NAC has a short half-life ≈2 hours with Cmax reached within an hour following oral administration. The PK data presented by the applicant is limited but is considered sufficient and acceptable given the nature of the application.

III.4 Toxicology

The applicant has submitted a general overview of the literature available on the toxicity of NAC. NAC is relatively well tolerated following acute administration with LD50 values in mice and rats ≥2250 mg/kg following IV administration (in buffered solution). Repeat dose studies of up to 52 weeks in dogs at doses up to 300 mg/kg and 28 weeks in rats at doses up to 1000 mg/kg did not report significant toxicity. Reproductive toxicity studies conducted in rats did not suggest a teratogenic risk but did report an effect on fertility at higher doses. These studies were not performed to GLP and only cursory information related to their conduct is contained in the submitted supporting literature. Wording noting that these studies were non-standard in nature has been included in section 5.3 of the SmPC and section 4.6 notes that animal studies with respect to reproductive toxicity are insufficient. The overview of toxicity submitted is limited but does not suggest any significant toxicological concerns and the submitted information is considered acceptable. The submitted Bonanomi (1980) study and acetylcysteine monograph (2002) state that NAC was negative for genotoxicity in an in-vitro Ames test. It is unlikely these studies were conducted to GLP but this is acceptable for an application on this legal basis.

III.5 Ecotoxicity/environmental risk assessment

No ERA was submitted with this application; this was considered acceptable.

III.6 Discussion on the non-clinical aspects

An abridged dossier was submitted in accordance with Article 10a of Council Directive 2001/83/EEC as amended. No new nonclinical studies were submitted. The non-clinical evidence in support of this application is based on relevant published scientific literature which is appropriate.

IV. CLINICAL ASPECTS

IV.1 Introduction

Trebon is presented as a powder for oral solution and each sachet contains 600 mg of N-acetylcysteine. Acetylcysteine is a well-known active substance with established efficacy and tolerability.

Oral acetylcysteine at a daily dose of 500 mg has been designated an ATC code of R05 CB01 (mucolytics).

The applicant sought an indication as a mucolytic therapy in chronic bronchitis and other respiratory conditions associated with the production of thick viscous mucus in adults. The presentation is a 600 mg sachet of powder for oral solution to be diluted in half a glass of water and consumed immediately. It is proposed that the product is used once daily. No specific restriction on the duration of therapy is proposed but the duration of use must be decided by the prescribing doctor. There is a clause in section 4.2 of the SmPC that states that the dosage may also be increased under the instruction of a doctor.

The applicant outlines that this active substance has been in medicinal use within the European Community for more than 10 years and has provided an extensive listing of such products authorised in Europe since 1973. No company studies have been performed by the applicant and so there is currently no requirement for a GCP inspection of any study sites. The applicant has instead performed a bibliographic review of acetylcysteine pharmacology, efficacy and safety studies published at Google Scholar, PubMed, Science Direct and Scopus. The majority of the published clinical studies of NAC in its mucolytic indication were conducted in Italy, few are recent studies.

PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

IV.2 Pharmacokinetics

Extremely limited pharmacokinetic data in the paediatric population have been provided (One study of NAC metabolism in malnourished children only). The proposed dose of 600 mg once daily in the 6-18 years age-group has not been justified and no information has been presented for key pharmacokinetic parameters in this age-group. The applicant has therefore restricted use of the product to adults only.

Pharmacokinetically, NAC may be viewed in one of two ways. The reduced form can be considered as the parent drug and all other forms considered metabolites. Or, all NAC, irrespective of redox status, may be considered as the parent drug. Borgstrom et al measured total NAC in deproteinized plasma (protein-bound NAC was not measured), whereas Olsson et al (1988) measured both reduced NAC and total NAC. Therefore, caution is required when making comparisons across studies, as well as applying the published data to the proposed product.

Some single dose PK data relating to the proposed dose (600 mg) have been presented. The applicant has outlined one study (Borgstrom et al 1990) of 600 mg NAC administered orally twice daily for 5 days. This repeated dosing of 600 mg NAC for 5 days did not result in accumulation.

NAC appears to be relatively rapidly absorbed when administered orally with a T_{max} of approximately 1 hour. Its bioavailability is low (~ 4-10%) due to significant first pass metabolism in the gut and liver.

Published V_{ss} values indicate distribution of NAC to extracellular water. The applicant has presented some very limited data that indicate orally administered NAC may distribute to lung tissue (Rodenstein 1978). The relevance of this study is not fully clear in a disease setting where levels of thick respiratory mucus are increased and absorption may be poor. This is particularly relevant for a drug with already low oral bioavailability.

Only 30% of administered NAC is excreted renally.

Olsson et al found the terminal half-life to be 6.25 hours following administration of 400 mg orally.

No data were presented by the applicant on the potential impact of the excipients sorbitol and polyethylene glycol 6000 on gastrointestinal transit time and absorption of the proposed product in the originally-submitted dossier. It was unclear if the bibliographic clinical data provided were fully applicable to this product as a result. This was raised as a Major Objection (MO) by the RMS at Day 70 and supported by the CMS (UK). This MO was finally resolved at Day 180. Some bibliographic and comparative data have been provided to support the assertion that absorption occurs in the upper part of the gastrointestinal tract. In published studies, the reported t_{max} lies between 30 min to 1 h in most studies and in no study does it exceed the 2 hours. Therefore, impact of excipients with osmotic effect may be minimised. The Trebon aqueous solution should aid a rapid absorption. Chen et al (2007) demonstrated that 5 g sorbitol had minimal impact on the AUC of metoprolol (another BCS Class 1 medicine). The applicant could not find any company/bibliographic data to confirm what percentage of NAC is absorbed in 15-30 minutes. The polyethylene glycol 6000 content of this product appears unlikely to impact the intestinal efflux of the proposed product. The applicant has also compared the polyethylene glycol content to that contained within authorised laxatives and other lower molecular weight PEGs to argue that osmotic laxative effects are likely to be negligible. The Yang et al (2017) and Jouet et al (2008) papers provided indicate that lower doses of PEG may not have significant impacts on MSITT. The applicant also highlighted the UK PAR for Mucolight 600 mg effervescent tablets [Authorised via Article 10(1)] and the fact that the MHRA did not require a BEq study despite the PEG 6000 content. The applicant made a reasonable argumentation that both the sorbitol and macrogol content should not impact the absorption of this medicinal product in a clinically relevant way. This medicinal product is not a narrow therapeutic index medicine where small changes in bioavailability could have a clinically significant effect.

IV.3 Pharmacodynamics

The mucolytic effect of NAC administered topically by nebulisation is thought to be due to a sulphhydryl disulphide interaction between NAC and mucus, leading to splitting of disulphide bonds in mucus molecules. The applicant has presented some very limited data that indicate orally administered NAC may distribute to lung tissue (Rodenstein 1978).

The applicant states that NAC has been reported to reduce the viscosity of sputum in both cystic fibrosis and COPD but no specific pharmacodynamic supporting data have been provided to justify this statement. Therefore, no recommendation for treatment in these specific conditions has been included in the Product Information.

Bridgeman et al (Thorax, 1994) found that despite the potential for antioxidant effects of NAC, respiratory tissue concentrations (BAL fluid or epithelial lining fluid) could not be achieved to result in a beneficial antioxidant effect in the setting of respiratory diseases such as COPD.

IV.4 Clinical Efficacy

Meta-analyses and systematic reviews indicate a modest benefit of NAC as a mucolytic agent in some respiratory disorders but the benefit in COPD remains uncertain, in particular at standard doses. More recent studies with better Jadad scores (higher methodological quality) show less of a benefit across respiratory disorders.

The 2015 Cochrane review by Poole et al found that there may be some limited benefit of NAC in Chronic bronchitis/COPD. However, the effects on exacerbations shown in early trials were larger than those reported by more recent studies, possibly because the earlier smaller trials were at greater risk of selection or publication bias. Therefore, benefits of treatment with NAC may not be as great as was suggested by previous evidence.

Cazzola's 2015 meta-analysis shows that treatment with NAC may possibly result in fewer exacerbations of COPD or chronic bronchitis. However, the meta-analysis was limited by the variety of definitions of acute exacerbations used across the included studies, making cross-study comparisons difficult. The authors did not observe a substantial difference in the results when the analysis focussed only on patients with a strict diagnosis of COPD using spirometric criteria. Again, when the studies focussed only on the effects of low dose NAC, the authors demonstrated that NAC was able to reduce the risk of exacerbations but this protective effect was more apparent in patients without a strict diagnosis of COPD made using spirometric criteria. However, NAC at high dose resulted in a significant effect, not only in patients with chronic bronchitis, but also in those with a validated COPD diagnosis. The administration of NAC at low dose provides a more marked risk reduction for the overall set of studies (without regard to the diagnosis) than that for the subset of studies with a validated COPD diagnosis. This suggests that a low dose is sufficient in providing benefit to patients with chronic bronchitis, but potentially not to patients with COPD. Overall, the strong signal that comes from Cazzola's meta-analysis is that if a patient has been diagnosed with COPD with an objective confirmation of airways obstruction, NAC should be administered at a dose of 1200 mg per day to prevent exacerbations, while if a patient has been diagnosed with chronic bronchitis but is without airways obstruction, a regular treatment with 600 mg per day seems to be sufficient.

In Chalumeau's 2013 Cochrane Review titled "Acetylcysteine and carbocysteine for acute upper and lower respiratory tract infections in paediatric patients without chronic broncho-pulmonary disease", the authors concluded the following."The results have to be interpreted with caution because they are based on a limited number of participants included in studies whose methodological quality is questionable. Acetylcysteine and carbocysteine seem to have a limited efficacy and appear to be safe in children older than two years. These results should take into consideration the fact that acetylcysteine and carbocysteine are prescribed for self-limiting diseases (for example, acute cough, bronchitis)."

Cazzola's 2015 meta-analysis indicates that the usefulness of NAC in exacerbation risk reduction seems to be evident in patients with a chronic bronchitis phenotype of COPD, mostly when it is administered at high dose.

Two of the relevant single studies (Not included in above systematic reviews or meta-analyses) found that 600 mg NAC once daily was ineffective in the management of COPD or Chronic Bronchitis. Two other single studies did show some benefit of NAC 600 mg once daily in COPD but these two studies had methodological flaws that precluded definitive conclusion.

In general, newer studies with a better study design indicate very limited benefit of NAC 600 mg once daily in COPD and Chronic Bronchitis.

No evidence has been presented that NAC has a beneficial impact on lung function in COPD.

There is some evidence of limited benefit of NAC administration for acute upper and lower respiratory tract infections in children aged 6 years and older who do not have underlying respiratory disease. However, no data to support a single dose of 600 mg per day in paediatric patients aged 6 years and older has been presented. Additionally, no robust efficacy data in children with underlying respiratory disease have been presented.

IV.5 Clinical Safety

In general, the safety profile of 600 mg once daily NAC in adults appears favourable.
No safety data in children ≥ 6 years of age and adolescents have been included in the dossier. No discussion or justification of the safety of the proposed formulation and dose of 600 mg once daily in children ≥ 6 years of age and adolescents has been provided. In MS IE, oral formulations of NAC delivering 600 mg per dose have not been authorised in children or adolescents as it is considered that such a strength is unsuitable in this age-group. This product was therefore considered unapprovable in children and adolescents and the Product Information has been amended to reflect this.

The most common adverse events observed in clinical trials were of a gastrointestinal nature e.g. nausea, vomiting, diarrhoea, abdominal pain and dyspepsia. It is noted that adverse skin reactions are reported with greater frequency than gastrointestinal adverse reactions in the post-marketing setting.

Hypersensitivity reactions to NAC have also been observed. It is not clear if these relate predominantly to intravenous use. The applicant stated they could not find any cases of hypersensitivity relating to oral NAC use as a mucolytic in the literature. Hypersensitivity is a medically important and unpredictable risk and so wording in the product information relating to bronchospasm and histamine intolerance was retained.

An absolute contraindication to use of NAC in children aged less than 2 years is justified based on the Chalumeau 2013 Cochrane review. Specifically, Chalumeau concludes (i) the size of the low risk of bias trial was not sufficient to provide enough statistical power to detect any rare potentially severe adverse event, (ii) many high risk of bias trials did not provide detailed descriptions of the severity of adverse events and abnormal laboratory tests or reasons for treatment discontinuation separately for each intervention group, and (iii) very few children under two years of age were involved in the studies.

No clinical data on the use of NAC in pregnancy or breast-feeding have been presented and so the Product Information was updated in line with the EMA's GUIDELINE ON RISK ASSESSMENT OF MEDICINAL PRODUCTS ON HUMAN REPRODUCTION AND LACTATION: FROM DATA TO LABELLING (EMEA/CHMP/203927/2005).

Risk Management Plan (usual pharmacovigilance requirements +/- additional requirements)

The Applicant has submitted a Risk Management Plan, version 1.1, dated 01/01/2019, 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 Trebon. The summary of the Risk Management Plan is as follows:

Safety Specification

Important Identified Risks	• Concomitant use with antitussives • Anaphylactic reactions and anaphylactic shock
Important Potential Risks	• Severe skin reactions (SJS and Lyell Syndrome) • Reduction in blood platelet aggregation • Use in patients with stomach and duodenal ulcers • Use in renal and hepatic impairment • Use in patients with asthma
Missing Information	• Use during pregnancy • Use during breastfeeding

Pharmacovigilance Plan
Routine pharmacovigilance activities are considered acceptable for Trebon. There are no additional pharmacovigilance activities.

Risk minimisation measures,
Routine risk minimisation measures are acceptable for Trebon. There are no additional risk minimisation measures.

Periodic Safety Update Reports (PSURs)

PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

IV.6 Discussion on the clinical aspects

N-Acetylcysteine is well known as an active substance which has been in use in clinical practice since the 1950s. Therefore, pharmacological, efficacy and safety studies have been published in the medical literature.

After oral administration NAC is likely quickly absorbed with a T_{max} of approximately 1 hour. Bioavailability has been shown to be low (4-10%) due to significant first-pass effect. Published V_{ss} values indicate distribution of NAC to extracellular water. The applicant has presented some very limited data that indicate orally administered NAC may distribute to lung tissue. Following oral administration, the elimination half-life is approximately 6.25 hours. Renal and hepatic impairment can reduce clearance and increase acetylcysteine plasma levels which may result in an increase in adverse drug reactions due to drug accumulation.

The mucolytic effect of NAC administered topically by nebulisation is thought to be due to a sulphhydryl disulphide interaction between NAC and mucus, leading to splitting of disulphide bonds in mucus molecules. Whether oral administration of Trebon can lead to this effect has not been confirmed.

Meta-analyses and systematic reviews indicate a modest benefit of NAC as a mucolytic agent in some respiratory disorders but the benefit in COPD remains uncertain, in particular at standard doses. More recent studies with better Jadad scores (higher methodological quality) show less of a benefit across respiratory disorders. There is no proven efficacy in cystic fibrosis, asthma or acute bronchitis.

The safety profile is well characterised and is reflected in the patient information. The main adverse events seen include hypersensitivity reactions, skin reactions and gastrointestinal effects.

Due to the physiological characteristics of children aged less than 2 years, the benefit risk balance of Trebon is considered negative in this group. The benefit-risk balance has also not been proven in adolescents and children aged 2-12 years due to the high NAC content in each Trebon sachet. Other formulations/products are more suitable in this age group.

Trebon is not recommended during pregnancy due to a lack of published reassuring data.

Taking all of the presented data into consideration, the benefit-risk balance of Trebon when used in adults as a mucolytic in chronic bronchitis and other respiratory conditions associated with thick viscous mucus hypersecretion is deemed to be positive. No conditions under Article 21a/22 of Directive 2001/83 are imposed.

V. OVERALL CONCLUSIONS

Based on the review of the data and the Applicant's response to the questions raised by the Reference Member State (Ireland) and Concerned Member State (United Kingdom) on quality, safety and efficacy, the RMS considers that the application for Trebon as a mucolytic therapy in chronic bronchitis and other respiratory conditions associated with thick mucus hypersecretion is approvable.

Oral acetylcysteine has been licensed in the European Union in similar indications since 1973 and so this active substance is well-characterised. The applicant has presented a review of the relevant published literature in accordance with Article 10a of Directive 2001/83/EC. As well as individual studies, both systematic reviews and meta-analyses have been published in relation to the use of NAC in respiratory conditions. While efficacy in the relevant conditions has been shown to be modest, the safety profile is acceptable. Gastrointestinal, skin and allergic side effects have been reported with use of this active substance.

A positive benefit-risk could not be concluded upon in paediatric patients aged 2-18 years, in part due to the higher strength of the formulation. An absolute contraindication has been concluded upon in paediatric patients aged less than 2 years on safety grounds. No clinical data on the use of NAC in pregnancy or breast-feeding have been presented.

The posology and method of administration are considered acceptable and are supported by data presented in the dossier. Oversight of treatment with Trebon by a doctor is required to ascertain suitability for and duration of treatment.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

In conclusion, the HPRA, on the basis of the data submitted, considered that Trebon 600 mg powder for oral solution demonstrated adequate evidence of efficacy for the approved indication as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

19.06.2025