CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Betahistine 2HCL DOC Generici 8 mg and 16 mg tablets
DOC Generici Srl, Italy

betahistine (as dihydrochloride)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1369/01-02/MR
Registration number in the Netherlands: RVG 101629, 101630

23 November 2009

Pharmacotherapeutic group:	antivertigo preparations
ATC code:	N07CA01
Route of administration:	oral
Therapeutic indication:	treatment of Ménière's syndrome
Prescription status:	prescription only
Date of first authorisation in NL:	13 February 2008
Concerned Member States:	Mutual recognition procedure with IT
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Betahistine 2HCL DOC Generici 8 mg and 16 mg tablets, from DOC Generici Srl. The date of authorisation was on 13 February 2008 in the Netherlands. The product is indicated for the treatment of Ménière's syndrome, symptoms of which may include vertigo, tinnitus, hearing loss and nausea.

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

Betahistine´s H_1-agonist activity at histamine receptors in peripheral blood vessels has been demonstrated in man by the abrogation of betahistine-induced vasodilation with the histamine antagonist diphenhydramine. Betahistine has minimal effects on gastric acid secretion (an H_2-receptor mediated response). Mechanism of action of betahisitine in Ménière's syndrome is unclear. The efficacy of betahistine in the treatment of vertigo may be due to its ability to modify the circulation of the inner ear or due to a direct effect on neurons of the vestibular nucleus.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator products Betaserc 8 and 16 mg tablets (NL License RVG 05852 and 13612, respectively), which have been registered in the Netherlands by Solvay Pharma B.V. since 1970 and 1989, respectively (original product). In addition, reference is made to the Betaserc authorisation in Italy (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Betaserc 16 mg tablets, registered in the Netherlands. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. These generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted, as this is not required for a generic application.
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II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is betahistine dihydrochloride (2HCl), an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The drug substance is a white to yellowish, crystalline, very hygroscopic powder. It is very soluble in water and soluble in ethanol. Betahistine 2HCl does not possess asymmetric carbon atoms. No polymorphs are known.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacture
Betahistine 2HCl sodium is prepared from two starting materials via a one-step synthesis and subsequent salt forming and purification processes. Adequate certificates of analysis of the starting materials and reagents have been provided. The drug substance has been adequately characterised.

Specification
The drug substance specification is in compliance with the Ph.Eur. monograph *Substances for pharmaceutical* use and with the Ph.Eur. monograph, with additional requirements for residual solvents. The specification is acceptable in view of the route of synthesis and the various ICH guidelines. Batch analytical data have been provided for 3 production scaled batches.

Stability
Stability data have been obtained during storage at 25°C/60% RH and 40°C/75% RH. The drug substance was adequately stored. The substance is stable at both conditions. Based on the stability data provided, the claimed retest period of 2 years, without storage conditions could be granted.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
One tablet Betahistine 2HCL DOC Generici 8 mg contains 8 mg Betahistine dihydrochloride, and 70 mg lactose monohydrate. Betahistine 2HCL DOC Generici 16 mg contains 16 mg Betahistine dihydrochloride and 140 mg lactose monohydrate. Both tablet formulations are fully dose proportional.

The tablets are packed in Alu/PVC/PVDC blister strips.

The excipients are: povidone K90, microcrystalline cellulose, lactose monohydrate, colloidal anhydrous silica, crospovidone and stearic acid. The composition of the 8 and 16 mg tablets is dose proportional, all excipients are well known and described in the Ph.Eur.

Pharmaceutical development
The development of the product is satisfactorily performed and explained. The excipients used are common in the manufacture of tablets and some are also present in the innovator product. The packaging materials are usual and suitable for the product at issue. The 16 mg tablets bear a score line. In breakability testing, all tablets were broken with three fingers of one hand, clearly demonstrating that ease of breaking is not an issue. Uniformity of mass was demonstrated on four batches divided into halves, all of which showed compliance with the Ph.Eur. requirement.

Dissolution tests
Dissolution tests were performed of the brand leader products in the Netherlands, Italy and UK/Ireland. The following can be derived from the dissolutio ndata presented:
- The dissolution of both proposed products is fast (over 90% in 25 minutes)
- The dissolution of the innovator batches is fast (over 90% in 15-20 minutes)
- Both strengths show similar profiles.

Comparative analysis results of the reference products, including impurities, are presented. The amount of impurities is always low (total amount less than 0.12%).

Manufacturing process
The tablets are prepared from a common granulate. The granulate is compressed. Each tablet strength has different markings and shape. The manufacturing process has been described sufficiently. The critical processes are defined and validation reports are enclosed for both manufacturers with production-scale batches. The process is shown to be consistent and yield a product complying with the specifications and showing good homogeneity.

Product specification
The product specification for the tablets includes tests for appearance, identification, disintegration, friability, hardness, assay, loss on drying, degradation, dissolution rate, related substances, mass, microbiological requirements and uniformity of dosage units. The proposed tests and requirements are acceptable. Batch analysis data have been provided on three pilot batches of each strength. Compliance with the release requirements is demonstrated.

Stability tests on the finished product
The tablets have been stored at 25°C/60% RH and 40°C/75% RH. An increase in loss on drying and degradation product is seen, as well as a decrease in hardness and disintegration time at both conditions. However, no out of specification is observed. The product is shown to be stable at long term and accelerated conditions. The claimed shelf-life of 3 years could be granted for the product stored in the original package.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
TSE certificates have been provided. Lactose monohydrate is the only excipient of animal origin. Stearic acid is obtained from a vegetable source.

II.2 Non clinical aspects

These products are generic formulations of Betaserc 8 and 16 mg tablets, which are available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of betahistine 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.

II.3 Clinical aspects

Betahistine dihydrochloride is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Betahistine 2HCL DOC Generici 16 mg tablets (DOC Generici Srl, Italy) is compared with the pharmacokinetic profile of the Dutch reference product Betaserc 16 mg tablet (Solvay Duphar B.V., the Netherlands).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results of reference products in different member states.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Study design
A single-dose, open randomised, two-way crossover bioequivalence study was carried out under fasted conditions in 24 healthy male volunteers, aged 20-31 years. Each subject received a single dose (16 mg) of one of the 2 betahistine formulations. The tablet was orally administered with 200 ml water after a fasting period of 10 hours. There were 2 dosing periods, separated by a washout period of 7 days. Blood samples were collected predose and at 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 10 and 14 hours after administration of the products. The analytical method is adequately validated and considered acceptable for analysis of the plasma samples.

According to the SPC, the tablets should be taken with food. This advice is based on improvement of gastric tolerability. For immediate release tablets, fasting is the most sensitive condition to measure bioequivalence. It is therefore accepted that the study was performed under fasted conditions.

Analytical methods
After absorption, betahistine is almost completely metabolised into the inactive metabolite 2-pyridyl acetic acid (2-PAA). Plasma samples were analysed for the inactive metabolite 2-PAA content by gas chromatography with mass spectrometric detection. The method was validated and a validation report was provided. As it was anticipated that the plasma levels of the parent would be very low after oral application due to a first-pass effect, no method was developed to measure the parent drug.

Results
All 24 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 2-PAA (inactive metabolite) under fasted conditions.

Treatment N=24	**AUC_{0-24h}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1475 ± 238	1560 ± 237	344 ± 107	0.67 (0.33 – 2.0)	3.1 ± 0.5
Reference	1471 ± 273	1551 ± 278	347 ± 117	0.67 (0.33 – 1.5)	3.0 ± 0.4
***Ratio (90% CI)**	---	1.01 (0.97 – 1.06)	0.99 (0.91 – 1.08)	---	---
CV (%)	---	9.4	17.1	---	---

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
$t_{1/2}$	half-life

**ln-transformed values*

The 90% confidence intervals calculated for $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of the inactive metabolite 2-PAA under fasted conditions, it can be concluded that Betahistine 2HCL DOC Generici 16 mg tablets and Betaserc 16 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

The 16 mg tablets are dose proportional with the 8 mg tablets. The pharmacokinetics of the metabolite 2-PAA are linear in the therapeutic range. Both strengths show similar dissolution profiles. The results of the bioequivalence study performed with the 16 mg tablets therefore apply to the 8 mg tablets. This extrapolation is in accordance with the NfG in Investigations of Bioavailability and Bioequivalence.

During the procedure, one member state raised Potential serious risks to Public health regarding the bioequivalence study. The MAH was asked:

- 1) why the parent drug (i.e. betahistine) was not measured in plasma (up to date sensitive bioanalytical methods were to be taken into account in the MAH's response)
- 2) to justify more precisely the reasons for the waiver to perform a bioequivalence study with the 8 mg strength
- 3) to justify why measurement of 2-PAA is a relevant parameter for demonstrating bioequivalence.

The MEB's assessment of the MAH's responses is discussed below in more detail.

1) It is well recognized, and also addressed comprehensively by the MAH, that the concentrations of betahistine in plasma are very low due to fast and nearly complete presystemic metabolism. The assumption that betahistine is subject to presystemic metabolism is based on C14-labelled betahistine studies, where almost the complete radioactive dose could be recovered in plasma and urine, but only the 2-PAA metabolite could be analysed.
The low recovery will of course not change if a very sensitive method, currently available is used.
Two aspects should be taken into account with respect to the use of the metabolite for establishing bioequivalence, which are offered by the NfG. Firstly, if betahistine is considered to be a prodrug and the active metabolites cannot be measured, except for an inactive metabolite, which shows linear pharmacokinetics, the use of the inactive metabolite is acceptable according to the new draft of the guideline on Bioequivalence testing. Secondly, taking into consideration that betahistine is rapidly and completely absorbed, and the very low concentrations of betahistine in plasma, as mentioned in the literature, it can be estimated that the absolute bioavailability of betahistine is very low (in the order of approximately 0.5 – 2%). This implies that the variability in the exposure of betahistine is probably very high and not suitable for establishing bioequivalence between two medicinal products. The variability will be too high to detect possible differences between the two products.
The inactive metabolite 2-PAA, which shows a 1000-fold higher exposure *in vivo* than the parent compound betahistine is considered more appropriate for establishing bioequivalence. The risk to public health by using this inactive metabolite for bioequivalence testing and subsequently registration of this product is considered marginal in comparison to using a sensitive analytical method for a compound with very variable pharmacokinetics due to very low bioavailability.

2) The MAH did clearly show that extrapolation from the 16 mg tablet to the 8 mg tablet is according to the NfG in Investigations of Bioavailability and Bioequivalence. All conditions mentioned in the guideline are applicable for this product:
- the pharmaceutical products are manufactured by the same manufacturer and process;

- the drug input has been shown to be linear over the therapeutic dose range.

Additionally, betahistine can be considered as a Class I drug in the Biopharmaceutical Classification system. According to the new draft of the guideline on Investigations of Bioequivalence, betahistine is considered a candidate for waiving *in vivo* bioequivalence studies.

3) This question is strongly related to the first question regarding the pharmacokinetic issue of using the inactive metabolite instead of the parent compound.

The exact working mechanism of betahistine is unknown. Different assumptions have been made regarding its mechanism of action. E.g. based on *in-vitro* data and pre-clinical animal data it can be concluded that betahistine induces indirectly histamine release by binding to H3 (histaminergic) receptors in the brain. The released histamine might improve microcirculation of the inner ear and reduce endolymphatic pressure. Other authors (Botta et al., Acta ORL Ital 2001;21:24-30) suggested that betahistine and its amino-ethyl-pyridine metabolite reduces discharge of vestibular cells in an inner ear preparation of a frog, thereby reducing the risk on vertigo. There seems to be no consensus which model is predominant for the clinical effect of betahistine. For an overview related to this issue see Jeck-Thole & Wagner, Drug Safety 2006;29:1049-59, and Lacour et al., Neuropsychiatric Disease and Treatment 2007:3(4) 429–40. It has also not been clarified how betahistine could be effective given that its bioavailability is extremely low and the major metabolite may be biological inactive.

It has however been shown in randomised controlled studies that betahistine has indeed a significant effect to a clinical relevant extent. E.g. in a recent study by Mira et al (Mira *et al*, 2003, Eur. Arch. Otorhinolaryngol 260:73-77), betahistine reduced the number of monthly vertigo attacks in patients with Ménière Disease from baseline (on average 7 attacks) with approximately 40% and 60% after 1 and 3 months treatment, versus 17% and 20% in the placebo arm ($p<0.05$ after one month and $P<0.01$ after 3 months). In addition, the safety profile of betahistine is favourable. Severe adverse events are extremely rare, and tolerance to common side effects like nausea may occur after prolonged use. This indicates that betahistine is not a narrow therapeutic drug.

Since efficacy of betahistine has been shown, it may be irrelevant to understand its underlying mechanism of action, and to what extent the parent drug is responsible for its pharmacodynamic effect. For many, especially ‘older’ products, its underlying mechanism is not understood, but this has never hampered acceptability of generic products thus far. Evaluation of bioequivalence based on the major metabolite in plasma is considered the best option, if the parent drug is very unstable and cannot be reliably measured. Even if bioanalytical methods would be applied with high sensitivity at picogram/mL levels, the levels of the parent drug would be too unstable to allow conclusions about differences of absorption between two products.

The answers provided by the MAH were considered sufficient by the concerned member state and therefore agreement was reached. Since the concerned CMS has referred this application to the CMD(h) as the only CMS and their major health concerns have been resolved, the referral procedure was finalised without a discussion in the CMD(h).

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk management plan

Betahistine was first approved in 1968, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of betahistine can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The SPC assessment was based on the innovator product Betaserc in the Netherlands. The chemical-pharmaceutical sections of the Dutch SPC are an adequate reflection of these product characteristics, otherwise the Dutch SPC is in line with the innovator SPC. The content is also in agreement with the MRP-SPC of NL/H/808/001-002 (Betarave 8 mg and 16 mg tablets).

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a first round with 10 participants. Based on the conclusions and recommendations from this first round, the MAH made some amendments to the package leaflet, which was then presented to ten respondents in the second test round.
The amendments made in several sections of the package leaflet led to a notable improvement in the scores on the questions in the amended sections.
In total, the number of respondents who gave a correct answer increased from 68% in the first round to 82% in the second round. The number of incomplete/ambiguous answers decreased from 15% in the first round to 7% in the second round. The quantitative improvements on readabililty were also reflected in the qualitative results. On the questions with a more open nature (for example: What is your first impression of the package leaflet?) an improvement was seen in the kind of responses in the second round. In the first round 60% responded positive on the package leaflet. In the second round 90% responded in a positive way. The MAH states that additional improvement can only be achieved by adjustment of the template.

The patient information leaflet has been adapted sufficiently taking into account the results of the tests. There were sufficient questions about the critical sections. The conclusions are clear, concise and clearly presented. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Betahistine 2HCL DOC Generici 8 mg and 16 mg tablets have a proven chemical-pharmaceutical quality and are a generic form of Betaserc 8 mg and 16 mg tablets. Betaserc is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

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

The SPC is consistent with the SPC of the Dutch innovator product, except for the chemical-pharmaceutical sections. The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other betahistine dihydrochloride containing product. Braille conditions are met by the MAH.

The Board followed the advice of the assessors. Betahistine 2HCL DOC Generici 8 mg and 16 mg tablets were authorised in the Netherlands on 13 February 2008.

During the procedure, one member state raised Potential serious risks to Public health regarding the bioequivalence study in which the inactive metabolite 2-PAA was used as parameter for demonstrating bioequivalence. These objections were resolved during a written procedure in which the MAH provided answers to the questions raised by the referent member state. Since agreement was reached during the MRP, and this member state was the only CMS, it was decided that discussion in the CMD(h) was not necessary.

The concerned member state, on the basis of the data submitted, considered that essential similarity has been demonstrated for Betahistine 2HCL DOC Generici 8 mg and 16 mg tablets with the reference product, and has therefore granted a marketing authorisation. The mutual recognition procedure was finished on 6 August 2008.

A European harmonised birth date has been allocated (16 May 1968) and subsequently the first data lock point for betahistine is December 2008. However, as these products will then not be marketed yet in the CMSs, there is no need to submit a PSUR in February 2009. The first PSUR will cover the period from August 2008 until December 2011. After which, the PSUR submission cycle is 3 years.

The date for the first renewal will be: 8 August 2013.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

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
Submission of a new or updated Ph. Eur. Certificate of Suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance. From a manufacturer currently approved.	NL/H/1369/ 001-002/IA/ 001	IA	28-9-2009	12-10-2009	Approval	N
Change in the name of the medicinal product in NL.	NL/H/1369/ 001-002/IB/ 002	IB	23-9-2009	26-10-2009	Approval	N