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Datasheet for the decision of 24 July 2023

Case Number: T 0258/21 - 3.3.07

Application Number: 12716828.4

Publication Number: 2694063

IPC: A61K31/4418, A61K9/107

Language of the proceedings: EN

Title of invention:
SHORT -ACTING DIHYDROPYRIDINES (CLEVIDIPINE) FOR USE IN REDUCING STROKE DAMAGE

Applicant:
Chiesi Farmaceutici S.p.A.

Headword:
Clevidipine for use in reducing stroke damage / CHIESI

Relevant legal provisions:
EPC Art. 56
RPBA 2020 Art. 13(2), 13(1)

Keyword:
Inventive step - main request, auxiliary request 1 (no)
Auxiliary requests 2a to 8a and 2b to 8b - admitted (no)

Decisions cited:
G 0002/21

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Case Number: T 0258/21 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 24 July 2023

Appellant: (Applicant)	Chiesi Farmaceutici S.p.A. Via Palermo, 26/A 43122 Parma (IT)
Representative:	Bianchetti & Minoja with Trevisan & Cuonzo IPS SRL Via Plinio, 63 20129 Milano (IT)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 25 September 2020 refusing European patent application No. 12716828.4 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chair	A. Jimenez
Members:	J. Lécaillon
	E. Duval

Summary of Facts and Submissions

I. The appeal was filed by the applicant (appellant) against the decision of the examining division to refuse European patent application No. 12 716 828.4 (hereinafter "the application").

II. The decision was a decision according to the state of the file based on the set of claims filed on 20 December 2018 and referring to three previous communications dated 5 April 2019, 26 June 2018 and 12 April 2017.

III. The following document D1 cited in these communications is relevant for the present decision:

D1: Abbie L. Erickson *et al.*, Pharmacotherapy, vol. 30, no. 5, May 2010, pages 515-528

IV. According to the communication dated 5 April 2019 which concerned the set of claims filed on 20 December 2018, the application did not meet the requirements of Article 83 EPC because the suitability of the claimed compounds for use in reducing ischemic stroke damage in a subject with an ischemic stroke was not sufficiently disclosed.

Furthermore, objections of lack of clarity, novelty and inventive step were raised in the communications dated 26 June 2018 and 12 April 2017 against the set of claims filed respectively on 18 October 2017 and with entry into the regional phase before the EPO.

V. With the statement setting out the grounds of appeal the appellant defended its case on the basis of a new

main request or, alternatively, based on a new auxiliary request 1 filed therewith.

VI. The following items of evidence were filed by the appellant with the statement setting out the grounds of appeal:

Annex 1: Adams *et al.*, Stroke, 38,1655-1711,(2007)
Annex 2: US 5,739,152
Annex 3: Polderman *et al.*, Neurocrit Care, 21:S161, (2014)
Annex 4: Brehaut *et al.*, Stroke, 46:AWP65, (2015)
Annex 5: https://www.stroke.org/en/about-stroke/types-of-stroke/ischemic-stroke-clots
Annex 6: https://www.stroke.org/en/about-stroke/types-of-stroke/hemorrhagic-strokes-bleeds

VII. In preparation for the oral proceedings, the Board issued a communication according to Article 15(1) RPBA 2020 dated 17 March 2023. In this communication the Board provided its preliminary opinion. In particular, the Board indicated that neither the main request nor auxiliary request 1 filed with the statement setting out the grounds of appeal appeared to meet the requirements of Article 56 EPC.

VIII. With the letter dated 27 June 2023, the appellant filed further auxiliary requests 2a to 8a and 2b to 8b and indicated the basis therefor in the original application. Further arguments in support of the patentability of the main request and the auxiliary requests were provided by the appellant in the letter dated 14 July 2023.

IX. The content of the claims upon which the present decision is based can be illustrated as follows:

Claim 1 of the main request read as follows:

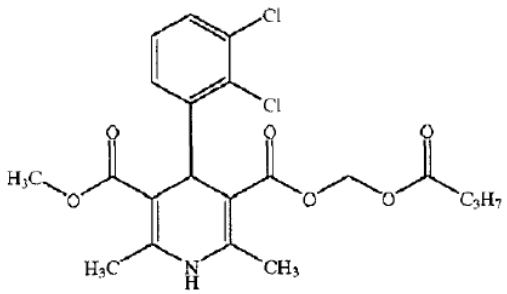
"1. A medicament comprising an effective amount of a short acting dihydropyridine compound wherein the short acting dihydropyridine compound is clevidipine or a pharmaceutically acceptable salt or ester thereof for use in a method of reducing ischemic stroke damage in a subject with an ischemic stroke, wherein the short acting dihydropyridine compound has a half-life in plasma of less than 30 minutes."

Claim 1 of auxiliary request 1 corresponded to claim 1 of the main request wherein the half-life in plasma was amended to "less than 2 minutes" and the following feature was added at the end of the claim:

"and wherein the medicament is an emulsion comprising 0.001-20 mg/ml clevidipine or a pharmaceutically acceptable salt or ester thereof."

Claim 1 of auxiliary request 2a corresponded to claim 1 of the main request wherein the formula of clevidipine was specified and the feature "or ester" was deleted. It read as follows:

"1. A medicament comprising an effective amount of a short acting dihydropyridine compound wherein the short acting dihydropyridine compound is clevidipine of Formula I



Formula I

or a pharmaceutically acceptable salt thereof for use in a method of reducing ischemic stroke damage in a subject with an ischemic stroke, wherein the short acting dihydropyridine compound has a half-life in plasma of less than 30 minutes."

Claim 1 of auxiliary request 3a corresponded to claim 1 of auxiliary request 2a wherein the following feature was added at the end of the claim:

"an onset of activity ranging from 2 to 4 minutes and an offset of activity ranging from 5 to 15 minutes."

Claim 1 of auxiliary request 4a corresponded to claim 1 of auxiliary request 2a wherein the following feature was added at the end of the claim:

"and the short acting dihydropyridine compound is administered at an initial dose ranging from 2 to 20 mg/hour."

Claim 1 of auxiliary request 5a corresponded to claim 1 of auxiliary request 2a wherein the following feature was added at the end of the claim:

"and the short acting dihydropyridine compound is administered at an initial dose ranging from 2 to 20 mg/hour to a maintenance dose from 4 to 6 mg/hour.

Claim 1 of auxiliary request 6a corresponded to claim 1 of auxiliary request 2a wherein the following features were added at the end of the claim:

"an onset of activity ranging from 2 to 4 minutes and an offset of activity ranging from 5 to 15 minutes and the short acting dihydropyridine compound is administered at an initial dose ranging from 2 to 20 mg/hour to a maintenance dose from 4 to 6 mg/hour."

Claim 1 of auxiliary request 7a corresponded to claim 1 of auxiliary request 2a wherein the following features were added at the end of the claim:

"and the short acting dihydropyridine compound is administered at an initial dose ranging from 2 to 20 mg/hour to a maintenance dose from 4 to 6 mg/hour and wherein the medicament comprises 0.5 mg/ml of clevidipine or a pharmaceutically acceptable salt thereof."

Claim 1 of auxiliary request 8a corresponded to claim 1 of auxiliary request 2a wherein the following features were added at the end of the claim:

"an onset of activity ranging from 2 to 4 minutes and an offset of activity ranging from 5 to 15 minutes and the short acting dihydropyridine compound is administered at an initial dose ranging from 2 to 20 mg/hour to a maintenance dose from 4 to 6 mg/hour and wherein the medicament comprises 0.5 mg/ml of clevidipine or a pharmaceutically acceptable salt thereof."

Each claim 1 of auxiliary requests 2b to 8b corresponded to each claim 1 of auxiliary requests 2a

to 8a respectively, wherein the feature "or a pharmaceutically acceptable salt thereof" was deleted.

X. Oral proceedings were held *per* video conference on 24 July 2023.

XI. The appellant requested that the decision under appeal be set aside and a patent be granted based on the basis of the main request or the auxiliary request 1, both filed with the statement setting out the grounds of appeal, or one of auxiliary requests 2a to 8a or 2b to 8b filed with the letter dated 27 June 2023.

XII. The arguments of the appellant, as far as relevant for the present decision, can be summarised as follows:

(a) D1 represented the closest prior art. The subject-matter of claim 1 of the main request differed from the one disclosed in D1 in that the management of hypertension with clevidipine occurred in a patient with a ischemic stroke to reduce ischemic stroke damage. As demonstrated in Annex 3 and Annex 4, clevidipine provided an optimal balance of efficacy, precision (titrability) and safety in ischemic stroke patients. Furthermore these documents substantiated an improved efficacy compared to other antihypertensive agents, in particular nicardipine, without the drawbacks thereof. The technical problem thus resided in the provision of a medicament for reducing ischemic stroke damage in ischemic stroke patients providing optimal balance of efficacy, precision (titrability) and safety with a higher activity and lower side effects than the other antihypertensive agents known in the art. The skilled person would have had no reasonable expectation in successfully

solving this problem with clevidipine, because the prior art was silent on the actual behaviour of clevidipine in ischemic stroke patients and this behaviour was unpredictable. As a result the main request fulfilled the requirements of Article 56 EPC.

(b) Claim 1 of auxiliary request 1 restricted in particular the half-life in plasma of clevidipine to less than 2 minutes. The same problem and solution approach was developed as for the main request. D1 did not suggest the use of clevidipine for reducing ischemic stroke damage characterized by an half-life in plasma of less than 2 minutes which would allow a rapid offset of action within 5-15 minutes.

(c) Auxiliary requests 2a to 8a and 2b to 8b were filed in reaction to the Board's preliminary opinion dated 17 March 2023 to overcome the objections of lack of compliance with the requirements of Articles 83 and 84 EPC and of Article 56 EPC raised therein. Moreover these auxiliary requests were *prima facie* relevant. They should therefore be admitted in the appeal proceedings.

Reasons for the Decision

Main request

1. Inventive step

1.1 Closest prior art

The appellant considered D1 as the closest prior art.

D1 relates to clevidipine for the management of hypertension (see title). It discloses the use of dihydropyridines for lowering blood pressure in hypertensive crises in intensive care units and emergency departments resulting from complications such as hemorrhagic stroke, cerebral ischemia, encephalopathy or myocardial ischemia (see abstract and pages 516, left column and right column, 1st paragraph). Dl concentrates on clevidipine and refers in particular to a study on clevidipine for the management of hypertension in patients with a hemorrhagic stroke (see Dl, page 526, right column, 2nd paragraph, 2nd sentence).

The Board agrees that Dl may be considered to represent the closest prior art.

1.2 *Distinguishing feature*

As argued by the appellant throughout the appeal proceedings, the claimed subject-matter differs from Dl in that the management of hypertension with clevidipine occurs in a patient with a ischemic stroke to reduce ischemic stroke damage.

1.3 Technical effect and objective technical problem

1.3.1 The Board observes that the original application does not provide any experimental data. No technical effect directly linked to the identified distinguishing feature, namely the reduction of ischemic stroke damage, has thus been demonstrated in the application documents. In this context, the Board underlines that the choice of clevidipine over nicardipine does not constitute the distinguishing feature over D1 as identified by the appellant.

1.3.2 In its letter dated 14 July 2023, the appellant referred for the first time to the achievement of "an optimal balance of efficacy, precision (titrability) and safety" mentioned on page 4 line 22 of the original application (see page 2, 4th paragraph under the heading "5.1. Main request", of the letter dated 14 July 2023). In the same letter, the appellant argued also that clevidipine would have higher activity and lower side effects than other hypertensive agents (see page 4, last paragraph of the letter dated 14 July 2023). In particular, it would not show the drawbacks in terms of hypoperfusion of nicardipine (see page 5, 1st paragraph of the letter dated 14 July 2023), which was indicated as preferred anti-hypertensive agent in case of acute ischemic stroke in D1 (see Table 1 of D1). According to the appellant these surprising effects would be substantiated by the post-published Annex 3 and Annex 4.

1.3.3 In the Board's view, the effect of an improved activity and reduced side-effects using clevidipine compared to other antihypertensive agents, in particular nicardipine in patients with specifically ischemic strokes, is not to be taken into account nor convincingly demonstrated, for the following reasons.

G 2/21 prescribes that "a patent applicant or proprietor may rely upon a technical effect for inventive step if the skilled person, having the common general knowledge in mind, and based on the application as originally filed, would derive said effect as being encompassed by the technical teaching and embodied by the same originally disclosed invention" (see Order 2.). Here, the Board notes that this effect was neither contemplated nor even suggested in the original

application. Indeed the original application did not mention any comparison to other anti-hypertensive agents and it encompassed the treatment of both hemorrhagic and ischemic stroke (see *e.g.* original page 3, 2nd paragraph). It follows that this technical effect relied upon by the applicant cannot be taken into account for the assessment of inventive step in accordance with G 2/21.

Moreover, even if said technical effect would have been derivable from the original application, the Board observes that Annex 3 and Annex 4 are merely abstracts reporting results of "ongoing" studies. These documents do not provide any detailed results nor any details on the protocols used. Merely average values for some properties of clevidipine and/or further anti-hypertensive drugs are provided. The meaningfulness of the appellant's exploitation of the data provided in these abstracts is therefore *prima facie* questionable. This applies in particular to the comparison between clevidipine and nicardipine based on Annex 4, heavily relied upon by the appellant. According to Annex 4, the results obtained for clevidipine are based on 13 patients (initially 10 patients and in addition 3 patients for which clevidipine was substituted to labetalol) while those for nicardipine are based on only 2 patients. The relevance of a comparison of average values obtained on each set of data is therefore limited. Furthermore, the study of Annex 4 appears to be a retrospective case study which was not designed as a clinical trial.

1.3.4 As to the balance of efficacy, precision (titrability) and safety, it is not necessary to examine whether this effect can be taken into account or is suitably demonstrated by annexes 3 and 4, because in any case

this effect does not modify the conclusion of the Board set out below. As a result, starting from D1, the objective technical problem may thus be formulated, as suggested by the appellant, as the provision of a medicament that can be used in a method of reducing ischemic stroke damage in a subject with an ischemic stroke (see statement of grounds page 8, 7th paragraph) which provides good balance of efficacy, precision (titrability) and safety (see page 2, 4th paragraph under the heading "5.1. Main request", of the letter dated 14 July 2023).

1.4 Obviousness of the solution

1.4.1 D1 suggests to use clevidipine to reduce blood pressure in patients with hemorrhagic stroke and Annex 1 discloses the potential benefits of reducing arterial hypertension in ischemic stroke.

In particular, Annex 1 highlights the need of a rapid reduction of blood pressure and at the same time of the potential for a rapid reversal to reduce the damage caused by the stroke while avoiding neurological worsening (see pages 1670-1672), *i.e.* to provide good balance of efficacy, precision (titrability) and safety. The skilled person aiming at solving the above defined technical problem would thus have been directed by Annex 1 towards an antihypertensive agent allowing a rapid reduction of blood pressure and at the same time a rapid reversal.

D1 provides several pharmacokinetics data for clevidipine (see *e.g.* Table 2, providing half-life, available concentration, initial and maintenance doses,...), reviews several studies on clevidipine and concludes that the advantages of clevidipine include

inter alia a short half-life, rapid onset and easy dosage titration (see paragraph bridging pages 526 and 527). As stated in the original application (see page 9 lines 5 to 7) easy dosage titration will contribute to ensuring a rapid reversal to avoid overshoot of hypotension. The skilled person would thus have learned from D1 that clevidipine has a rapid onset and offset of activity and is thus suitable to allow a rapid reversal. It therefore fulfills the criteria defined in Annex 1. The properties of clevidipine reported in D1 furthermore correspond to the results provided in Annex 3 and Annex 4 (rapid onset and offset of activity, easy titration and low administration volume in view of concentration and administration doses), which cannot thus be seen as unexpected.

Hence, the Board considers that the skilled person would have had a reasonable expectation of success of reducing ischemic stroke damage in a patient with ischemic stroke with clevidipine and thereby providing good balance of efficacy, precision (titrability) and safety in view of D1 together with Annex 1.

1.4.2 The appellant argued that the present solution would not be obvious since D1 did not relate to ischemic stroke and hemorrhagic and ischemic stroke would present many medical differences.

The Board disagrees.

As argued by the appellant, the etiology of the hemorrhagic and ischemic strokes is different as well as the stroke damages. However, in both cases reduction of blood pressure *per se* is known to be beneficial.

Furthermore Annex 1 is directed to the management of patients with specifically ischemic stroke. The properties indicated in Annex 1 for a good antihypertensive candidate for reducing ischemic stroke damage, namely rapid onset of activity and rapid reversal, constitute properties of the antihypertensive drug *per se* which have been found to be beneficial in said treatment. There is no indication that these properties are only to be found when reducing hypertension in patients with ischemic stroke.

1.4.3 In its letter dated 14 July 2023 and during oral proceedings, the appellant also argued that D1 would not provide any indication of the actual behaviour of clevidipine in patients with ischemic stroke, which was not predictable. On the contrary D1 did not disclose clevidipine in the list of antihypertensive agents in the treatment of acute ischemic stroke, but only labetalol or nicardipine along with its risk of hypoperfusion.

The Board firstly observes that since inventive step is under discussion and the treatment of ischemic stroke is the distinguishing feature, it is evident that D1 does not provide any data for clevidipine specifically in patients with ischemic stroke. Furthermore, D1 is not a review on various antihypertensive agents and their applications but it focuses on clevidipine. The passage on other antihypertensive agents including table 1 belongs to the introductory part of D1 presenting the background of the review. Contrary to the appellant's argument provided during the oral proceedings, the skilled person would not understand this passage as teaching away from using clevidipine in patients with ischemic stroke. As stated above, Annex 1 defines properties of antihypertensive drugs *per se*

which, according to Annex 1, would be beneficial in the treatment of hypertension in patients with ischemic stroke. These properties are intrinsic properties of the antihypertensive drug and the skilled person would expect them to occur independently of the health status of the patient to which it is administered.

In this context, the Board underlines that, should the appellant's unpredictability approach have been followed (*i.e.* the effect of clevidipine in the treatment of ischemic stroke damage in patients with ischemic stroke not be considered plausible on the basis of Annex 1 and D1), an issue of lack of sufficiency of disclosure would have arisen since the original application does not provide any experimental data substantiating the claimed medical use.

1.4.4 The appellant also stated in the letter dated 14 July 2023 that Annex 1 confirmed the impossibility of determining an unambiguous relation between the mechanism of action and how exactly the blood pressure in patients is lowered. The appellant referred to the passage on page 1671, left column, 2nd-3rd paragraphs of Annex 1 which concludes that "the appropriate treatment of arterial hypertension in the setting of acute ischemic stroke remains controversial".

The Board observes that the passage on page 1671 referred to by the appellant concerns the overall question of managing hypertension *per se* in patients with ischemic stroke and under which conditions (which threshold of systolic blood pressure to start anti-hypertension treatment from, setting of thrombolytic therapy in relation to hypertension management,...). It remains that if hypertension management was to be used, then the rapid onset and ability for a rapid reversal

are recommended independently of any particular mechanism of action of a specific antihypertensive drug (see paragraph bridging pages 1671-1672).

1.4.5 Finally, the fact that, as underlined by the appellant during the oral proceedings, D1 mentions remaining potential drawbacks with clevidipine (see page 525 left column last full paragraph) does not undermine the combined teaching of D1 and Annex 1 with respect to the expectation of success of solving the problem posed, because these drawbacks are side effects not related to the properties at interest to solve the problem posed.

1.4.6 In the Board's view, the skilled person would therefore have considered obvious to use clevidipine to reduce ischemic stroke damage in a subject with an ischemic stroke whereby providing good balance of efficacy, precision (titrability) and safety.

1.5 Accordingly, the subject-matter of claim 1 of the main request does not comply with the requirements of Article 56 EPC.

Auxiliary request 1

2. Inventive step

2.1 The additional features of claim 1 of auxiliary request 1 are generally disclosed in D1. Clevidipine is already known from Dl to have a half-life of less than 2 minutes (see table 2), to be formulated as an emulsion (see "Safety and Tolerability", page 525) and be available at a concentration of 0.5 mg/ml (see Table 2).

2.2 Furthermore the appellant did not provide any particular effect which would be linked to one of these features and would be unexpected over D1. In particular a rapid offset of action is already generally described in D1 and is considered to be an intrinsic property of clevidipine.

2.3 It follows that the reasoning developed under item 1. for claim 1 of the main request applies *mutatis mutandis* to claim 1 of auxiliary request 1.

2.4 Hence, the subject-matter of claim 1 of auxiliary request 1 does not meet the requirements of Article 56 EPC.

Auxiliary requests 2a to 8a and 2b to 8b

3. Admittance

3.1 Auxiliary requests 2a to 8a and 2b to 8b were filed on 27 June 2023, *i.e.* after notification of the summons to oral proceedings dated 10 October 2022, and substantiated, as regards inventive step, only in the letter dated 14 July 2023, *i.e.* 10 days before the oral proceedings. Their admittance must be decided on the basis of Article 13(2) RPBA 2020. According to Article 13(2) RPBA 2020, requests filed at such a late stage of the appeal proceedings shall, in principle, not be taken into account unless there are exceptional circumstances, which have been justified with cogent reasons by the party concerned.

3.2 The Board observes that the appellant did not provide any such exceptional circumstances during the written proceedings. During the oral proceedings, the appellant explained that these auxiliary requests had been filed

in reaction to the Board's preliminary opinion dated 17 March 2023 to overcome the objections of lack of compliance with the requirements of Articles 83 and 84 EPC and of Article 56 EPC raised therein. Moreover these auxiliary requests were *prima facie* relevant. In particular, with regard to inventive step, the purpose was to include further features supported by Annex 3 and Annex 4 and better reflect the difference in mechanism between hemorrhagic and ischemic strokes.

3.2.1 As stated in the communication of the Board according to Article 15(1) RPBA 2020 dated 17 March 2023 and reiterated during oral proceedings, the issue of inventive step over D1 was already raised in the communication of the examining division dated 12 April 2017 (see page 2, 2nd paragraph) and 26 June 2018 (see pages 3 to 4). Hence, the lack of inventive step raised in the preliminary opinion of the Board cannot *per se* provide exceptional circumstances in the sense of Article 13(2) RPBA 2020 justifying the late filing of the requests about a month before the oral proceedings, let alone their substantiation even later.

The appellant has furthermore not elaborated on the reasons why the features introduced to overcome the lack of inventive step issue would better reflect the difference in mechanism between hemorrhagic and ischemic strokes. This is not straightforward since these features are at least generally disclosed in D1 for clevidipine in the context of hemorrhagic stroke (see below item 3.2.2). Hence this does also not provide exceptional circumstances in the sense of Article 13(2) RPBA 2020.

3.2.2 Moreover, contrary to the opinion of the appellant, auxiliary requests 2a to 8a and 2b to 8b are not suitable to resolve the issue of inventive step on file (Article 13(1) RPBA 2020) for the reasons developed in the following paragraphs.

In auxiliary requests 2a and 2b merely the references to salt and/or ester of clevidipine were deleted. These modifications have no impact on the reasoning of lack of inventive step developed for the main request, which applies therefore *mutatis mutandis*.

The additional features introduced in auxiliary requests 3a to 8a and 3b to 8b are generally disclosed in D1 as follows:

- onset of activity from 2 to 4 minutes and offset of activity from 5 to 15 minutes in auxiliary requests 3a, 3b, 6a, 6b, 8a, 8b (see D1 page 518, left column, first full paragraph and paragraph bridging pages 526 and 527 generally disclosing a short-acting antihypertensive agent with rapid onset of action and easy titration),
- initial dose ranging from 2 to 20 mg/hour in auxiliary requests 4a to 8a and 4b to 8b (see D1, table 2 disclosing an initial dose of 1-2 mg/hour),
- maintenance dose from 4 to 6 mg/hour in auxiliary requests 5a to 8a and 5b to 8b (see D1, table 2, disclosing a maintenance dose of 4-6 mg/hr), and
- concentration of clevidipine of 0.5 mg/ml in auxiliary requests 7a, 7b, 8a and 8b (see D1, table 2, availability as 0.5 mg/ml in 50- or 100-ml vials).

As no particular effect directly linked to these features and not already derivable from D1 has been substantiated, it is not immediately apparent how these

features could support an inventive step of the claimed subject-matter.

3.3 As a result, auxiliary requests 2a to 8a and 2b to 8b are not admitted into the appeal proceedings (Article 13(2) and 13(1) RPBA 2020).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chair:

B. Atienza Vivancos A. Jimenez

Decision electronically authenticated