

The Patents Act, 1970

Section 25(1)

In the matter of the application for
Patent No. 2571/del/1998 filed on
28th Aug. 1998.

And

In the matter of representation
under section 25(1) of the Patent
Act, 1970 as amended by Patent
(Amendment) Act, 2005.

And

In the matter of rule 55 of the Patent
Rules, 2003, as amended by the
Patent (Amendment) Act, 2005.

M/s Pfizer Product Inc. ,USA The Applicant

M/s Torrent Pharma Ltd., India The Opponent

Hearing held on Sept 18,2007

Present

Mr. Deepak Mundra Agent for the Applicant

Mrs. Ranjan Mehta Dutt

M/s Rajeshwari.H Agent for the opponent

DECISION

A representation by way of opposition under section 25(1) of the Patent Act, 1970, as amended by Patent (Amendment) Act, 2005, was filed by M/s K & S Partners on behalf of M/s Torrent Pharmaceuticals Ltd. on 15 September, 2005 with a request for hearing under rule 55 of the Patent Rules, 2003 as amended by Patent (Amendment) Act, 2005. The applicant submitted their reply statement and evidence on 5th October, 2006. The hearing was fixed on 18th Sept. 2007 and both the parties to the opposition attended the hearing on the scheduled date.

The application for patent claiming priority of USA dated 29 August, 1997 was filed by M/s Pfizer Product Inc. , USA , on 28th Aug., 1998 for an invention titled "therapeutic combination". This application claiming a composition comprising amlodipine and atorvastatin or their pharmaceutical salt. was allotted the application number 2571/del/1998.

Opponent in their written submission taken eight grounds under section 25(1) for opposing the present application. However, during hearing they argued on the following grounds and the applicant also countered on those grounds only. I have, therefore taken up only those grounds argued by both the parties during hearing and give my considered opinion on those grounds only. The grounds taken up for arguments by the opponent are

- (1) Lack of novelty under section 25(1) (b),(c)
- (2) Lack of inventive step under section 25(1) (e)
- (3) Not patentable under section 25(1)(f)
- (4) Insufficiency of description under section 25(1)(g)

Now I shall consider the grounds argued by the opponent one by one & countered by the applicant subsequently. Opponent submitted during hearing that the claims are drawn to a composition comprising amlodipine and atorvastatin or their pharmaceutically acceptable salts. Such a combination was

disclosed by the press release dated May 20, 1997 (Annexure A) and which has been admitted by the applicant. This was made prior to commencement of the Anglo-Scandinavian Cardiac outcomes Trial (ASCOT). The press release states "ASCOT also will examine whether the combination of the lipid lowering agent Lipitor (Atorvastatin Calcium) tablets with NORVASC (trade name for amlodipine) reduces the rates of heart attacks or strokes." Therefore it is evident that the above publication which was made in the press without any obligation of confidentiality, disclosed to the public the combination of atorvastatin calcium with amlodipine besylate, which is the same combination/composition being claimed in the present application. The opponent to strengthen their argument in favour of anticipation referred to Narayan's Book Page 371.

"The essential test is pose as long as long ago in 1862 Hills VEVANS 4 DE GF & J., 288 at 30% (1862) 31 LJ Ch 457 at 463: namely, whether the information found in the prior document about the process is, for the purpose of practical utility, "equal to " that contained in the claims in the Patent is suit."

It is clear that the composition / combination comprising amlodipine /atorvastatin was clearly, unambiguously & explicitly disclosed by the above press release and therefore the present application stand anticipated by the said disclosure.

In respect of **lack of inventive step** the opponent argued that the claimed composition is for the treatments of atherosclerotic coronary heart disease . For the management of it coronary heart disease it is necessary to manage all the four factors responsible for it ie., accumulation of cholesterol , oxidized low density lipoprotein, triglyceride rich lipoprotein and smooth muscle proliferation. The applicant has vide page 4 in para 3 of the specification has admitted that " for a meaning fully reduce the risk of coronary heart disease, it is important to manage the entire risk spectrum."

Opponent further argued that atorvastatin was known as lipid lowering agent . The applicant has acknowledged on page 1, para 3 that atorvastatin calcium

is an inhibitor of HMG-COA and is a potent lipid lowering compound disclosed in US 4681893 as well as US 5273995 granted & published in the year 1993.

Further on page 2 of the specification the applicant has acknowledged that amlodipine and related dihydrophyridine compounds disclosed in US 4572, 900 & US 5155,120 published in 1992 are long lasting calcium channel blocker. Thus by the year 1992, 1993, amlodipine & atorvastatin salts were known in the public domain. The combination of these two compounds i.e., Amlodipine & Atorvastatin was well known prior to 1998 from the following facts.

(1) There were many researchers during the period 1992-95 who believed that management of atherosclerotic heart disease perhaps requires a combination of drugs. The British Hypertension Society (BHS) proposed a study for patients having high blood pressure and high cholesterol to study the impact of lipid lowering and cholesterol lowering agent. This design of the study is depicted in table on page 75 of the opponent submission vide annexure F wherein it clearly depicts combination of calcium channel blocker with statin. Therefore it is clear from the above, that the researcher did have the idea that statin may be combined with calcium Channel blockers for effective management of atherosclerotic vascular diseases.

(2)an article by ***D.M. Kramsch et al. Journal of Human Hypertension , 1995 vide annexure 'G'*** . The author stated in that article that so far the treatment of atherosclerosis has focused on decreasing low density lipoprotein cholesterol , however the same has been effective only in 50-60% of the patients. The reason appears to be that the other factors ie., oxidised LDL, triglyceride rich ldl & unopposed smooth muscles cell proliferation. It further clarifies that the solutions to this problem is :

“ ...that lipid lowering therapy has limited efficacy and there is therefore a need for other drugs especially anti-proliferative agent for secondary and primary prevention”. To test this hypothesis, a new calcium antagonist, amlodipie was studied..... These data suggests that amlodipine may be an excellent candidate in combination with lipid

lowering drugs, for dual therapy of atherosclerotic vascular diseases and may also be effective as monotherapy even when LDL-C is not lowering satisfactorily.” The author concludes. **“....In conclusion, amlodipine appears to inhibit SMC (Smooth Muscle Cell)proliferation and monocyte/macrophage infiltration by blocking Ca²⁺ movement with cells & preventing LDL-oxidation..... Their data indicates that amlodipine may be effective both-as an adjunct to lipid lowering drugs and as monotherapy in altherosclerotic vascular diseases.”** Opponent argued that the study of kramsch make the following conclusion (1) the current therapy focusing on lipid lowering /cholesterol lowering alone is not sufficient for management of atherosclerotic vascular disease (2) Amlodipine has complementary mechanism to lipid lowering therapy (3) combination of amlodipine with lipid lowering agent would be effective. The opponent further argued that **Jukema et.al. Atherosclerosis, Thrombosis and vascular Biology, 1996**, wherein Jukema has reviewed the claimed data made available by the **Regression Growth Evaluation Statin study (Regress) trial**. The relevant passage----.”**Although the REGRESS trial suggest strongly that addition of CCBs to 3-hydroxy-3-methylglutaryl-coenzyme reductase inhibitor therapy (Pravastatin) acts synergistically in retarding the progression of established coronary atherosclerosis.”**. Thus clearly indicating that the combination therapy of lipid lowering drug with calcium channel blocker should synergistically acts in retarding the progression of atherosclerosis.

Although Jukema acknowledges the limitation of calcium channel blockers and understand the prevailing perception of possible adverse effect of calcium channel blockers. On page 132 of the said document Jukema understands the limitation that the REGRESS trial was not designed to study the effect of Calcium Channel blockers with lipid lowering agents. However despite this Jukema finds that the report, **“provides substantial evidence that calcium channel blockers may have a beneficial effects on the evaluation of coronary atherosclerosis in patients treated with lipid lowering therapy**

and Jukema recommends that further trial should be conducted to validate the merit of the combination. Therefore it can be concluded from the data discussed by Jukema that (1) calcium Channel blockers would work effectively in combination with lipid lowering agents (2) combination of amlodipine with lipid lowering agents/statin would be effective as combination therapy for management of atherosclerosis vascular heart disease.

(3) Another evidence on which they argued for lack of inventive step is the applicant's press release on May 20, 1997. Wherein the applicant announces that they would be conducting a randomized clinical trial to evaluate the combination therapy of amlodipine besylate with atorvastatin calcium. The trial (ASCOT) design vide para 6 states.

“ASCOT will also examine whether the combination of lipid lowering agent lipitor (atorvastatin Calcium) tablets with NORVASC reduces the rates of heart attack & strokes. A secondary goal of the study is to compare health care cost for patients treated with news agents to the cost for those treated with older one.”

From the above it is clear that following teachings were available to a person skilled in the art.

- (a) amlodipine besylate is a long lasting calcium channel blockers (published 1993)
- (b) Atorvastatin is a known lipid lowering agent (published 1992)
- (c) Data suggests that amlodipine may be effective as a monotherapy or as adjunct with lipid lowering agents for treatment of atherosclerotic heart decease (kramsch et al publish 1995)
- (d) Combination of lipid lowering agent with calcium channel blockers recommended for treatment of atherosclerosis since the combinatory ingredient would augment each other in the therapy and retard atherosclerosis (Jukema et al published 1996) & recommended for further trial .
- (e) Trial for evaluation of effect of combination of amlodiopine besylate and atorvastatin calcium via ASCOT (published May 20 1997).

These prior art teach unambiguously and explicitly that a combination of amlodipine and atorvastatin would be useful in the treatment/ management of atherosclerotic vascular disease . After the teaching of Jukema et.al & Kramach et.al. the conduct of the trial of 1997 was to verify whether the hypothesis proposed on the basis of limited data by Jukema & Kramach worked on larger population. The very fact that a clinical trial was undertaken on large number of human beings itself is a evidence of the fact that the hypothesis proposed by Jukema & Kramach was very strong and applicant was very sure of the positive outcome. The trial was in fact only to verify on a larger population the hypothesis that worked on smaller population of monkeys.

Therefore, the opponent argued, the prior art prevailed between 1992-97 gave a clear direction to a person skilled in the art that this combination of amlodipine & atorvastatin alone would work to retard althersclerosis . It motivated a skilled person to come up with the claims as in the present application. The hypothesis and the data was extremely strong to propel a skilled person into preparing the composition as claimed in the present invention.

The opponent further argued under the ground of **‘Not an invention/not patentable’ under section 3(d) & 3(e)**. The claims 1 to 13 are drawn to a composition/combination essentially comprising amlodipine or its pharmaceutically acceptable salt (amlodipine besylate) and atorvastatin or its pharmaceutically acceptable salt (hemi calcium salt of atorvastatin). A composition vide section 3(d) cannot be patented unless any significant therapeutic efficacy over the parent substance is shown. There is not evidence in the body of specification any therapeutic efficacy of the said combination. The composition of claims 1 to 13 essentially a combination of atorvastatin calcium salt & amlodipine besylate which is already disclosed and no statement of enhanced efficacy. Therefore, composition of claim 1 to 13 are not patentable under section 3(d) of the Act.

Under section 3(e) the opponent argued that the claims of the present invention are not patentable since the claim 1-13 relates to a composition

comprising atorvastaion or its pharmaceutically acceptable salt and amlodipine or its pharmaceutically acceptable salt in admixture with an inert pharmaceutically acceptable carrier /diluent or excipients. Since the composition relates to a substance which is a mere admixture, resulting in aggregation of properties of the components thereof. The component of the composition i.e. active ingredients are amlodipine besylate and atorvastatin hemi calcium salt. Amlodipine besylate performs its usual function i.e. acting as a calcium channel blockers and atorvastatin hemi calcium salt performs the usual function of lowering of lipid level. Given that the said combination does not result in any enhanced additive effect because not a single example in the entire specification demonstrates the said composition provides surprising result. Therefore the composition/combination claimed in claim 1-13 is a mere collocation of the properties of the individual ingredients. The specification describes elaborate clinical trial to be conducted etc. but does not provide any data as to the effects of the trial . The applicant has submitted in their reply statement an annexure II which provides certain in vitro data and tried to demonstrate that the composition as claimed is synergistic .Para 7 to 9 clearly states that the stock solutions individually of amlodipine or atorvastatin have been prepared and used for their purposes of the experiment & there is no indication in the annexure that the said combination is synergistic. Also the opponent argued that such further data submitted in annexure II in the reply statement, even if is relevant, cannot be taken on record as of now. They referred to Cipla vs Glaxo Case wherein it was held that **“.....unexpected bonus effects not described in the specification can not form the basis for a valid claim of this kind If a synergistic effort is to be relied on, it must be possessed by everything covered by the claim and it must be described in the specification**” Therefore the claim 1 to 13 are not patentable under section 3(e) of the Patent Act.

On the **ground of insufficiency**, the opponent submitted that the amended claims are not sufficiently described by the Complete specification and the method by which it is to be performed. The claim are drawn to a

composition comprising atorvastatin & amlodipine. As stated above & as evident from page the 34-35 of the specification, the applicant intends to cover a composition as well as combination of these compounds. The example are drawn to combination . The examples provided are only speculative as they state that a trial will be conducted. The results of the purportedly synergistic combination is not set out. In view of that, the application & the claim fail on this ground as well.

Now I shall discuss the argument and submission put forward by the applicant during hearing. In respect of **novelty & inventive step** together the submission of the applicant is that the opponent's arguments are based on supposition and extrapolation from the prior art and not what is actually set forth in prior art. The applicant argued that when prior art contains apparently conflicting references each one must be weight to determine its significance in context, and as to what really tells to skilled person. Thus all the prior art must be balanced, relative to each other, to assess properly the inventive step. A prior art references may lead the skilled person away from the invention or discourages to follow the path suggested in the reference or if it suggest that the development flowing from reference's disclosure is unlikely to lead to a productive solution to the relevant problem. Therefore it is very important to see the invention in its proper context and to have an understanding of the whole technical back ground to the invention by considering all reference including those which might lead the skilled person away from the claimed invention. When the state of the art at the priority date of the application is reviewed, with these principles in mind it can be such that (Aug, 1997) calcium Channel blockers such as amlodipine were viewed unfavorably. There was much evidence to suggest that one would not obtain a favorable outcome by combining CCBs such as amlodipine with other drug including statin like atorvastatin . Even if it is agreed that the skill man could conclude from the state of the art at the date of the priority of this application, that further evaluation and testing were needed including the subject invention's specific

combination of amlodipine and atorvastatin, no conclusion could properly be drawn as to the likely outcome of such combination.

The applicant further referred to the unfavorable perception of CCBs in the 1990, which motivated against their use in combination. By the mid 1990, influential group of physicians and epidemiologists published series of articles in journals using clinical studies, created a highly unfavorable atmosphere for using CCBs for blood pressure management causing a significant drop in their use.

The negative perception of CcBs start in fact from 1989 when Yusuf & Furberg in their publication concluded that CCBs do not reduce the initial or recurrent myocardial infraction when given routinely to patients with acute myocardial infraction or unstable angina.

The negative perception of CCBS was dramatically escalated in 1995 by Held & Yusuf by presentation in meetings. Such as ***“Pharmacamon Daros 1995” & 35th Annual conference on cardiovascular disease Epidemiology and prevention held in San antonia Taxas.*** This created concern among physicians & pharmaceutical regulatory authorities regarding long term safety and benefit of procardial XL (nifedipine) and Norvasc (amlodipine). The ***American Heart Association congress in November 1995*** included a debate regarding negative effect of CCBs. During the same time many a article published related to the use of CCBS to excessive GI bleedings , surgical bleeding and cerebral damage. In addition CCBS were not held promising in the treatment of coronary artery diseases. The above described negative perception of CCBS began to change only after the priority date of the applicant with publication of high quality long term CCBs trial. Therefore at the priority date of the application the person skilled in the art would have tended to avoid CCBs & not have motivated to look for combination product which involves the use of CCBs such as amlodipine.

Accordingly the applicant asserted that the amlodipine was approved and used for treating hypertension and atorvastatin was approved & used for treating hyperlipidemia does not mean that they were both prescribed in

combination. In view of above argument the opponents contention under clause (b) of section 25(1) should be rejected.

Applicant further argued against opponent claim that the combination claim lack inventive step over annexure B. In may 1997 a large scale press release announcing the intended trial was issued. The applicant argued that it was the intention to administer NORVASC (Containing amlodipine besylate as active agent) to patient in combination with ACE inhibitors. Actually it was the tertiary objective to examine whether the combination of the lipid lowering agent lipitor (atorvastatin calcium) tablets with NORVASC (amlodipine) reduces the rate of heart attack or strokes. This is also evident from the posters presented by Prof server of Imperial College London, describing ASCOT at the **WHO/ISH Blood pressure Lowering Treatment Trialist Collaboration symposium**. one of the parties refers to a tertiary objective of the ASCOT study as being “ **to evaluate whether synergistic effect on total coronary or cardiovascular events are observed in association with the use of atorvastatin & amlodipine.**” Neither annexure A nor Annexure B provided any date that would have predicted any preferred or expected result or supported the proposition that such synergistic efforts might be observable. Also the fact that an examination of the co-administration of Norvasc and Lipitor was included as only a tertiary objective of the trial indicates that their was no particular expectation of success for this in the treatment of cardiovascular disease. The very need for its inclusion in the study emphasize that the effort of the co-administration of the drug was still unknown at the time. The Annexure A & B do not provide sufficient motivation with reasonable expectation of success for a skilled person in the art to prepare dose form of amlodipine & atorvastatin. Therefore the said state of the art, lead to no conclusion as to the likely outcome of the evaluation of the combination and therefore the combination of the present invention does not lack in inventive step.

During the hearing, the opponents argued against the reply submission of the applicant.

- (1) That “a person skilled in an art would not attempt to combine amlodipine since the scientific community at that point of time has the notion that amlodipine would cause adverse effect, such as cancer.”; the opponent said that all the prior art regarding negative notion prevailing during the relevant period is misplace. None of the prior art, relied upon by the applicant deal with amlodipine, there are publication regarding nifedipine, isradipine or other compounds which are all short adding calcium channel blockers. None of the prior art citation relied upon by the applicant state that amlodipine has any adverse effect or cannot be combined with lipid lowering agents.
- (2) To the defence, taken by the applicant that, the combination of amlodipine & atorvastatin would induce drug interaction which may result in unexpected toxic side effect , the opponent argued that cytochrome P450 is a family of enzymes which is responsible for metabolism of many drugs. CYP3A4 is the most abundantly expressed P450 in human liver. They argued that the drug interaction occurs usually when two drugs compete for the same enzyme substrate and limited amount of substrate is available. A person skilled in the art knows that there is very low possibility of competition between two drugs for this enzyme since CYP3A4 is available in plenty. Therefore there is not rise of one drug inhibiting or inducing the activity of the particular CYP to profoundly impact, the metabolism, the plasma concentration and rate of clearance of the other drug that are metabolized by the same CYP. Thus in the present case context the defense of the applicant is misplaced or misconceived.

The opponent submitted that the prior art fully & completely discloses the combination / composition as claimed. In case of combination it is the concept which is important. The prior art teaches the combination fully what has been claimed is merely a verification of the prior art & no patent can be granted for such verification.

The opponent also replied to the T694/92 case, relied upon by the applicant. On the issue of inventive step. The applicant argued that the reasonable expectation of success should be present in the prior art teaching.

The opponent argued that the said decision is totally inapplicable in the present case. The said case was drawn to a process for genetically modifying a dicot plant & wherein one of the step was involved deletion of a particular protein i.e. phaseolin. In that case the prior art disclosed all the elements, there was no teaching for modifying and developing the genetically modified plant and such art of genetically modified plant cell was not yet routinely established & the absence of reasonable expectation of success was primary due to uncertainty of the art at that time & therefore the process adjudged inventive. In the present case facts are completely different.

Atorvastatin & amlodipine are individually disclosed by the prior art disclosure & successfully marketed. The evidence generated by the prior art was clearly convincing that the combination would be useful in the treatment of atherosclerotic vascular disease. Finally the announcement of clinical trial based on hypothesis generated by Jukema & Kramsich was sufficient to prove that there was more than reasonable expectation of success for this combination.

Applicant also argued against the opponents submission in respect of **ground of 3(d)** and submitted that the invention relates to a novel composition and is not a new form of known substance. It is a novel composition which has increased therapeutic efficacy than the sum of the effect achieved by administering the ingredients separately.

The applicant also denied the opponent's argument that the composition of the present invention is a mere admixture and therefore not patentable under section 3(e). The invention exhibit synergistic effort in relation to the benefit of the invention in treating cardiovascular disease, is demonstrated by references to the effort of combination of amlodipine and atorvastatin on the production of nitric oxide by endothelial cells which has a important role in vascular biology. A deficiency in bio availability of Nitric Acid can result in normal vasodilation which enhance Nitric Acid synthesis, therefore have beneficial effect.

In respect of **insufficiency of description** the applicant argued that the opponent's argument that the specification does not describe the preparation of the composition is not true. Composition described can be easily prepared by those skilled in the art using the conventional method of preparation. Further it mentions the percentage of the active compounds in the composition. The specification also describes, the types of diluents/carrier to be used. The opponents doubt about the synergistic effect of the combination of amlodipine & atorvastatin are baseless as has been explained to substantiate against 3(e) of claimed by opponent. Therefore opponent arguments are not sustainable & are liable to be rejected.

Now having gone through the arguments & submission of the parties to this case, I shall now give my considered opinion on each of the grounds raised & argued. Opponent argument that the press release of May 1997, wherein para 6, says “ ***ASCOT will also examine whether the combination of the lipid lowering agent lipitor tablets with Norvasc ie.,amlodipine besylate reduces the rate of the heart attack and strokes.***” Therefore the combination of atorvastatin calcium & amlodipine besylate was disclosed to the public. The present invention is drawn to a composition comprising atorvastatin & amlodipine & their pharmaceutical acceptable salt in a given range of rates to each other along with conventional carrier/diluents.

Now a claimed invention lack novelty unless it includes at least one essential technical feature distinguishing it from the prior art. In my opinion what has been placed before me show that all the technical feature of the present invention has not been made available to the public or in other words all technical features of the composition have not been made available to the public. The combination of Amlodipine besylate (2.5 mg to 160 mg) & Atorvastatin calcium (2.5. mg to 160 mg) ie.,in a specific dose combination as mentioned in claim 1 of the present invention was not found disclosed in any single document or prior art. I am therefore of the considered view that in the

light of all the technical feature of the present invention with respect to the prior art, the claims of the present invention are novel.

In order to find out whether the instant invention is obvious to a person skilled in the art, the historical development before the invention has to be analyzed. At the time of the filing of this invention following subject matter were available as a prior art.

- (a) Atorvastatin was known as a lipid lowering agent. Applicant also admitted that atorvastatin calcium is an inhibitor of HMG-COA & this compound was disclosed in US 4681893 & 5273995 granted & published in 1993
- (b) Amlodipine besylate was known as a long lasting calcium channel blocker and this compound & its related dihydropyridene compounds were known vide US 4572909, US 5155120 the later published & granted in 1992.
- (c) At the time of the filing of this application the common general perception among the researchers & physicians, around the world was that atherosclerotic coronary heart disease are caused by various factors e.g accumulation of cholesterol, oxidized low density lipoprotein, triglyceride rich lipoproteins and smooth muscle cell. It was generally believed that plaque accumulation in arteries which eventually forms a thrombotic mass & migrates to block blood vessels & where the tissues does not receive the blood supply, it dies. Therefore for adequate management of atherosclerotic coronary heart disease it is necessary to manage all the four factors. The applicant has also admitted in their specification that “ for meaningfully reducing the risk of coronary heart disease, it is important to mänge the entire risk spectrum.”
- (d) The British Hypertension Society in the year 1993, proposed a study on the basis of above perception, for which it planned to enroll patients having high blood pressure & high cholesterol and study the impact of lipid lowering agent and cholesterol lowering agent by using

a combination of calcium channel blocker and statin. Therefore this was an idea with the researcher in the year 1993 that statin in combination with calcium channel blocker might be effective for the management of atherosclerotic vascular diseases.

- (e) D.M. Krams in an article in Journal of Human Hypertension, 1995 stated that the current practice of lipid lowering / cholesterol lowering alone is not sufficient for the management of atherosclerotic vascular disease. The author clarifies “that lipid lowering therapy has limited efficacy and there is therefore a need for other drugs especially anti-proliferative agents for secondary and primary prevention. To test this hypothesis a new calcium antagonist, amlodipine was studied-----”. These data suggest that amlodipine may be an excellent candidate in combination with lipid lowering drugs, for dual therapy of atherosclerotic vascular disease and may also be effective as monotherapy even when LDL-C is not lowered satisfactorily”, Finally the author concludes “ ---In conclusion amlodipine appears to inhibit SMC proliferation and monocyte / macrophage infiltration by blocking calcium ion movement into cell and preventing LDL-oxidation-----the data indicate that amlodipine may be effective both as an adjunct to lipid lowering drugs and as monotherapy in atherosclerotic vascular diseases”, clearly indicating Amlodipine has a complimentary mechanism in the lipid lowering therapy and therefore combination of amlodipine with lipid lowering agent would be effective.
- (f) A report of data generated during the REGRESS (Regression growth Evaluation station study) clinical trial, evaluated the combined administration of calcium channel blocker & pravastatin in the treatment of atherosclerosis ,showing synergistic effect (Jukema Circulation 1995, 92 N0.8, Suppl 1-197)
- (g) Jukema (Arterioscler. Thromb. Vas. Biol, 1996, 16, 425-430) on page 426, col 2, reported the synergistic effect obtained with the

combination of amlodipine & pravastatin. Further to Jukema papers, Orekhov, (Cardiovascular Drugs & Therapy, 11,1997,350) further reported the more pronounced anti-atherosclerotic effect of the combination of amlodipine & lovastatin as compared to the administration of the individual compounds. As amlodipine acts synergistically with both pravastatin and lovastatin, this would motivated the skilled person to the combination of the amlodipine with the newest and the best statin , atorvastatin.

- (h) ASCOT, posters presented by Prof. Peter Sever, May 1997, purposes amlodipine and atorvastatin to be given together to evaluate the synergistic effect.
- (i) Orekhov, et al international Journal of Cardiology, 1997, 62, Suppl 2, s-67-77, gave a clear one way street direction to use the combination therapy in view of the beneficial result obtained therein, thus inviting the skilled person to further investigate on the combination therapy with other statin such as atorvastatin with amlodipine.
- (j) In the opposition proceedings in the corresponding EPO application, one of the opponent drawn the attention to the fact that B-hydroxy acid form of HMG-COA reductase inhibitors are crucial part in the inhibition of the enzyme HMG-COA reductase. As this B-hydroxy moiety is also present in atorvastatin, the essential & common chemical structure of all the active statin make their mode of action clear & predictable. It would motivate to replace lovastatin with atorvastatin in view of the beneficial & superior effect as shown by Bertolini (Atherosclerosis 130,1997, 237-44) which teaches the superior effect of atorvastatin & compared to pravastatin in the treatment of hypercholesterolemia. Davidson (Am.J Cardiol, 1997, 79(11) 1475-81) teaches a significantly higher reduction in LDL cholesterol, triglyceride, total cholesterol and apoB compared to lovastatin & concludes that atorvastatin is highly effective and well tolerated by the patients. Similarly Dart et.al Am. J.Cardiol 1997,

80(1),39-44) reveals-the direct comparison between atorvastatin & simvastatin in patient with hyper cholesterolemia with the result that 46% of the patients achieve LDL cholesterol target goal by 16 weeks compared to 27% of the patient treated with simvastatin.

Here it is pertinent to state that the applicant's argument of unfavourable drug-drug interaction against their combination is an after thought put forward to highlight the Jukema et.al opinion which teaches away from the combination of a statin (Pravastatin) amlodipine as the patient receiving the combination experience more adverse clinical effect as compared to the patient receiving the statin alone. However any experimental data against drug-drug interaction being adverse , has not been reported in any prior art data.

On the other hand Lea (Drugs May 1997, 828-847) shown that as atorvastatin has the highest mean elimination half-life (14 Hrs.), its use in the combination would be preferred by the skilled man having the choice under the known statin compounds. More over the present invention does not provide any kind of evidence of which demonstrates that the claimed compound is able to treat atherosclerotic vascular disease , hypertension, hyper lipidemia, angina pectoris , myocardial infraction, cardiac arrerst , Cardiac ischaemia etc. Therefore, experimental data does not provide any technical information beyond what is known before the priority data of the present application 29/08/1997. The present invention provide nothing but an analogous use of a combination without any inventive ingenuity. If an invention has been alleged to be obvious & did not involve any inventive step and it is found or conceded on analysis that there is a difference between that which has been proved to have been published and used and that which forms the subject matter of monopoly, if the opposition is to succeed, it must be shown that the differences between the two clearly have been obvious & does not involve any inventive step. Here what is available in the

prior art etc. are shown in para (a) to (j) & on comparisons with what is the subject matter of the present invention I find that the difference between the two is very obvious and does not involve any inventive step. When deciding, whether an invention is obvious, it is often necessary to decide whether a particular avenue of research leading to the invention is obvious. The research paper protocol of clinical trial and other analysis as mentioned above clearly indicated that there existed a fairly good and reasonable expectation that a person skilled in the art might get good result from trying that avenue of research. The applicant in the EPO while replying against the objection of lack of inventive step stated that lower portion of chemical structure of pravastatin & lovastatin contains a hexahydronaphthalene, whereas atorvastatin lower portion contains a heterocyclic pyrrol ring attached to multiple aromatic ring. This structural difference, proving that the statins are quite dissimilar in physico-chemical properties and therefore the extrapolation with a reasonable expectation of success from the prior art statin is not possible. In contrast to this the attention was drawn to the fact that the B-hydroxy acid form of HMG-COA reductase inhibitors are crucial part in the inhibition of enzyme HMG-COA reductase. This B-hydroxy moiety is present in atorvastatin, this essential & common chemical structure of all active statins make their mode of action predictable and would motivate to replace lovastatin with atorvastatin in view of the beneficial effect. The fact that the B-hydroxy acid moiety found in statins are crucial part in the inhibition of the HMG-COA reductase, has been admitted by the applicant also. Further Lea (drugs, May 1997, 828-847) has shown that atorvastatin has the highest mean elimination half life (14 hrs.), therefore its use in combination would be preferred by the skilled person having the choice under the known statin compound. In the face of these contradictory arguments, it is difficult to believe the applicant's claim

that the “extrapolation from the prior art statin ie., pravastatin & lovastatin to atorvastatin is not possible with reasonable expectation of success.”

Also a combination may be obvious combination but it will not be obvious if it would be safe or it would represent an advance on what-had gone before. This will be dependent upon the clinical trial which was not foreseeable. In this case through it was a reasonable prediction for the skilled man having regard to the known properties of amlodipine and atorvastatin that the combination would be safe and efficacious.

Therefore on the basis of argument of the parties , discussed above, the prior art available on the date of filing of this application , I am of the considered opinion that the present invention is obvious and does not involve an inventive step with respect to prior art available.

In respect of not an invention, opponent claim that claims 1 to 13 is not patentable under section 3(d). A composition cannot be patented unless any significant therapeutic efficacy is shown over the parent substance. Now in the specification I found that the said application does not provide any kind of evidence to demonstrate that the claimed composition is able to provide any proof of enhanced efficacy beyond the known efficacy of the individual compounds .

Therefore my considered opinion is that the present invention fails to prove the enhanced efficacy against the combined efficacy of the individual component of the composition as is evident also from the body of the specification.

In respect of synergistic effect, the claim of the opponent that the composition relates to a substance which is a mere admixture resulting in aggregation of the properties thereof. The alleged active ingredients are amlodipine besylate and atorvastatin hemi-calcium salt. Amlodipine besylate acts as calcium channel blocker and

atorvastatin hemi calcium salt acts as lipid lowering agent. The combination provide relief from hypertension and hyperlipidemia which is known in the art and therefore does not show any synergistic effect. The applicant justified the synergistic effect by submitting a report with reply statement where it has described that the combination of amlodipine and atorvastatin produces and unexpected synergistic effect on the stimulation of Nitric oxide (No) in isolated human endothelial cells as compared to the individual component produces when taken separately (control).

Although there is nothing in the body of specification to show any synergistic effect for the combination of the present invention however the experimental data provided by the applicant with reply statement proved that the combination of Amlodipine and atorvastatin stimulated nitric oxide production from human endothelial cells in a synergistic fashion . This synergism was never substantiated by the applicant and I do not know whether such effect was at all known to the applicant either at the time of filing, I therefore can not agree that the combination of the present invention has synergistic effect and which was not clearly predicted by prior art in different analysis & report.

In respect of insufficiency of description the examples given in the body of specification are speculative in nature which provide the protocol etc to be followed for clinical trial.No therapeutic effect has been shown or justified. Synergism of the combination/composition has also not been proved. During the opposition proceedings, the applicant submitted the experimental data ie., after 10 years of filing of the present application. I am of the considered view that this specification falls short to stand on its own in the matter of sufficiency.

On summing up all the grounds which I have discussed & gave my considered opinion , are (a) that the present invention is

novel over the prior art (b) it is obvious and lack in inventive step with respect to the prior art and publications available (c) It is not patentable under section 3(d) and 3(e) and (d) the application failed to justify the sufficiency of description to a certain extent.

Therefore on the basis of the arguments made by the parties on those grounds stated above as well as on the basis of the circumstances of this case, I conclude that the present invention is not patentable I therefore refuse to proceed with the application 2571/del / 98 for grant of patent.

Application stand disposed with no cost to either party.

On this date 3rd of February, 2009.

S.K. ROY

Asstt. Controller of Patents & Designs

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