(2013) 06 IPAB CK 0007

In the Intellectual Property Appellate Board

Case No : Miscellaneous Petition Nos. 18, 19/2011, 65/2012 In OA/15/2011/PT/MUM

Ranbaxy Laboraties Ltd. — APPELLANT

Vs

Controller of Patents & Designs, The Assistant Controller of Patents & Designs And Syngenta Ltd. — RESPONDENT

Date of Decision : 12-06-2013

Acts Referred:
Patent Act, 1970 — Section 25(2)(b), 25(2)(g), 25(2)(f), 25(3)(e)

Citation : (2013) 2 MIPR 259

Hon'ble Judges : Prabha Sridevan, J;V. Ravi, Technical Member

Bench : Division Bench

Advocate : S. Majumdar, Ranjana Mehta Dutt, Debashish Banerjee

Final Decision : Dismissed

Judgement

Prabha Sridevan, J

1. This appeal is against the dismissal of the opposition to a Patent Application No. 113/MUM/2000 under the ""A Non-Interacting Drug Combination

for Treating Hyperlipidaemia in Mammals"". The granted patent No. 212310 was published on 25.01.2008. It was filed on 04.02.2000 originally bearing

titled ""Drug Combination"" claiming priority from three U.K. Applications all of the year 1999. Post grant opposition was filed. An opposition Board

was constituted and the opposition board recommended that the ground under Section 25(2)(b) was established by the opponent, the ground under

Section 25(2)(g) was not established. However, the Opposition Board said that S. 25(2)(e) which is obviousness and Section 25(2)(f) was established

by the opponent. The Controller held that the present invention was novel since no single document anticipated the invention and the person skilled in

the art would not have found the invention obvious and that the prior art cannot be used to arrive at the present invention. The Controller also held that

the invention did not fall under the provisions of Section 25(3)(d) or (3)(e) and therefore the objection relating to Section 25(2)(f) was not established.

In these circumstances, the Controller did not accept the recommendation of the Board and rejected the opposition.

The invention is this:

The invention concerns safe non-interacting drug combinations of a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, which is

(E)-7-[4-(4-flurophenyl)-6-isopropyl-2-[methyl (methylsulfonyl) amino]pyrimidin-5-yl](3R,5S)-3-5-dihydroxyhe pt-6-enoic acid or a pharmaceutically

acceptable salt thereof (the Agent) and a drug which is either an inducer, inhibitor or a substrate of cytochrome P450, in particular cytochrome P450

isoenzyme 3A4. Particular combinations are useful in treating hyperlipidaemia in humans who are receiving immunosuppressive chemotherapy. A

preferred combination is the Agent and a fibrate drug, the use of such a combination in treating hyperlipidaemia in mammals, and medicaments

containing such as combination for use in such treatments.

HMG-CoA reductase inhibitors are the most widely used prescription medication for the treatment of hyperchloesterolaemia.

The first generation statins (such as lovastatin, pravastatin and simvastatin - prodrug derivatives of fungal metabolites - and fluvastatin) are

categorized in that they achieve only a limited cholesterol lowering affect before the dose administered is limited by elevations in serum ALT. Second

generation ""suprestatins"" (such as atorvastatin - synthetic compounds-structurally distinct from first generation compounds) inhibitors are categoriesed

in that they lower cholesterol levels to a much higher degree than the earlier first generation of statins before their dose is limited by serum ALT

levels. Atorvastatin has been successful over the first generation of statins. Since its launch in the USA atorvastatin has reached sales in 1998,

doubling from 1997, of $2.2 billion, capturing 38% of new prescriptions for cholesterol lowering agents in the US and is now the most widely

prescribed hypolipidaemic agent in the US (Warner-Lambert 1998 annual results).

The specification speaks of adverse events reported for statins in general.

Myopathy and rhabdomyolysis have been particularly associated with taking a statin in combination with gemfibrozil, niacin, cyclosporine or

erythromycin, (Hunninghake H. Et al. Current Opinion in Lipidolgy (1992), 3, 22-28) which are all substrates for P450 isoenzyme 3A4. The increase in

adverse events associated with taking a combination of a statin drug with one of the other drugs mentioned above is probably due to a drug: drug P450

isoenzyme 3A4. Therefore when a drug which is also metabolized by P450 3A4 is administered alongside a statin which also is metabolized by P450

3A4, the side effects discussed above are more likely to occur. Increase in the side effects, such as muscle damage, is thought to be due to elevated

statin levels in muscle cells inhibiting farnesylation and geranylgeranylation of muscle proteins.

A major disadvantage of the currently available ""Super Statin"", atorvastatin, is that atorvastatin is metabolized by cytochrome P450 enzymes, in

particular 3A4, which may cause drug interactions with other drugs which are inducers, inhibitors or substrates of the same P450 enzyme which

metabolises atorvastatin.

Since the possibility of drug interactions was unacceptably high, the invention refers to a statin that belongs to the class of what was known as super

statin and calls it the agent.

The agent is disclosed in European Patent Application, Publication No. 0421471, and in Bioorganic and Medicinal Chemistry, (1997), 5(2), 437-444 as

an inhibitor of HMG-CoA reductase which is a major rate-limiting enzyme in cholesterol biosynthesis. The agent is described as useful in the

treatment of hypercholesterolaemia, hyperlipoproteinaemia and atherosclerosis.

The agent is not metaboised by cytochrome P450 3A4 and therefore does not possess the same potential for drug interaction shared with the currently

available ""super statin"", i.e. atorvastatin, or any of the other currently available statins.

2. The specification defines several terms:-

By the term ""non-interacting drug combination"" we mean a drug combination for which there is no adverse affect to the patient by its administration

through the mechanism of drug metabolism by cytochrome P450 isoenzyme 3A4. it is recognized that in certain instances a drug interaction may

nevertheless occur between two such drugs when in combination through a

completely different mechanism not involving drug metabolism, such as

affecting drug absorption.

Whether a drug is an inhibitor, inducer or substrate of a P450 enzyme can be easily determined by procedures known to the skilled person. Such

procedures may involve the exposure of a radiolabelled drug to hepatocytes or hepatocyte microsomes or isolated P450 enzyme and the use of

analytic techniques, such as HPLC, in determining metabolite formation. A specific procedure is described herein.

By the term ""combination"" we mean either that the Agent and the drug of the combination and administered together in the same pharmaceutical

formulation or that the agent and the drug are administered separately. When administered separately components of the combination may be

administered to the patient simultaneously or sequentially.

We have found that the agent is not metabolized significantly by the major cytochrome P450 isoenzymes 1A2, 2C9, 2C19, 2D6 and 3A4. This is

further feature of the invention.

3. The complete specifications give what are the preferred combinations in which the Agent is combined with a drug which includes fibrates or drugs

which are used in treating cardiovascular conditions and which includes cyclosporine and/or tacrolimus.

4. The specifications also mentioned that features of the invention include dosage.

Other features of the invention include those described above wherein the agent is used at doses of 5 to 80 mg per day. When a dose range of 5 to 80

mg per day is referred to herein for the Agent other particular dosage ranges, which are further independent aspects of the invention, include (as

appropriate) 10 to 80 mg per day, 10 to 60 mg per day, 10 to 40 mg per day, 5 to 40 mg per day, 5 to 20 mg per day, 10 to 20 mg per day, 20 to 60 mg

per day, 20 to 40 mg per day and 40 to 60 mg per day. Particular dosages are 5, 10, 20, 40 and 80 mg per day. A particularly suitable starting dose of

the agent in the methods referred herein is 5 to 10 mg per day, especially 10 mg per day.

5. The specification for the experimental procedures that were done and the assessment of data.

FOR TREATING HYPERLIPIDAEMIA AND ASSOCIATED CONDITIONS IN POST

TRANSPLANT PATIENTS RECEIVING

IMMUNOSUPPRESSIVE THERAPY

Two common drugs used in suppressing the human immune system, cyclosporine and tacrolimus (formerly called FK506), are known to be

metabolized by cytochrome P450 3A4. In particular cyclosporine is also a known inhibitor of P450 3A4 and is therefore likely to reduce the

metabolism of any other drug which is metabolized by P450 3A4. Therefore where immunosuppressive therapy is prescribed, such as with the drugs

cyclosporine and tacrolimus (especially cyclosporine), the attendant physician must be cautious as to any other therapy which may be jointly presented

to the patient in combination. Immunosuppressive therapy is most commonly used before, during and after human transplant operations. In particular

with cardiac transplants the attendant physician may wish to also place the patient on statin drug therapy to reduce future incidents of coronary heart

disease, stroke, peripheral arterial occlusive disease or peripheral vascular disease, particularly in patents with elevated cholesterol or in

normolipidaemic patients with other risk factors associated with heart disease. In particular within this special patient group (human transplant

pateitns), the patients are at high risk of developing accelerated atherosclerosis in the transplant organ in an aggressive fashion and within a short

period of time due, in part, to the surgical damage to the blood vessels during transplantation, any previously underlying untreated conditions and the

immunosuppressive therapy. Hyperlipidaemia is common after transplantation even in patients who did not suffer hyperlipidaemia prior to

transplantation, incidence 60-80% of recipients.

We have discovered that the agent is extremely effective at treating hypercholesterolaemia in patients following transplantation and that the agent is

not metabolized by cytochrome P450 isoenzyme 3A4. Therefore we have found through the use of the agent in a clinical study that the agent may be

conveniently dosed to patients who are undertaking immunosuppressive therapy without any clinically significant side effects associated with the

concomitant dosing of the agent and the immunosuppressive drug(s) and, in addition, also achieve much higher levels of cholesterol lowering than has

previously been achieved, such as by the use of pravastatin.

And also describes a particular types of patients undertaking immunosuppressive

chemotherapy who may benefit from the method of the invention.

As a further of the invention, and due also to the fact that the agent is not metabolized to any significant extent by P450 isoenzymes, it is possible to

administer, more safely than before, to a patient receiving immunosuppressive therapy a fibrate and the agent. As discussed earlier the administration

of a fibrate and a statin has previously been associated with a higher incidence of rhabdomyolysis and myopathy. In addition fibrate drugs do interact

with cyclosporine due to both being metabolized by the same P450 isoenzyme. Therefore, the use of a statinand a fibrate drug in combination with

immunosuppressive therapy was previously contraindieated due to the likelihood of possible serious interactions (Hunninghake 1992, Wanner C.

Kidney Int. (1995) 52 (suppl.) S60-S62; and Katznelson S. Contributions Nephrol. (1997) 120, 97-104). However, if possible, it would be advantageous

to also administer a fibrate alongside a statin since fibrates are known to lower different lipoproteins than statins and therefore their combined

pharmacology would be complementary in reducing even further the likelihood of CHD and other diseases mentioned above associated with the

formation of atherosclerosis. Therefore the possibility of combining the agent, which is not metabolized by lowering cholesterol to a greater extent in

such patients than previously achieved and more safely than could previously be achieved by the administration of a statin, a fibrate and an

immunosuppressive drug.

Accordingly, the present invention relates to a non-interacting drug combination comprising a first drug, HMG-CoA reductase inhibitor, which is (E)-7-

[4-(4-fluorophenyl)-6-isopropyl-2-methyl (methylsulfonyl) amino[pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically

acceptable salt thereof and a second drug which is an inhibitor, inducer of substrate of P450 isoenzyme 3A4 of the kind such as herein described, with

ratio percentages of first drug: second drug from between 0.25:99,75% w/w and 99.5:0.5% w/w.

Accordingly, the present invention relates to a pharmaceutical formulation comprising a non-interacting drug combination as claimed in any of the

preceding claims, wherein it comprises (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-methyl (methylsulfonyl) amino[pyrimidin-5-y l](3R,5S)-3,5-

dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof, a drug

which is an inducer, inhibitor or substrate of P450 isoenzyme 3A4

and a pharmaceutically-acceptable diluent, carrier or adjuvant of the kind such as herein described.

6. The complete specifications give a non-limiting example of a clinical trial in which the subjects were 40 men and women post cardiac transplant.

This describes the trial and duration of the treatment.

The Claims are as follows:-

1. A non-interacting drug combination comprising a first drug, HMG-CoA reductase inhibitor, which is (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-methyl

(methylsulfonyl) amino]pyrimidin-5-y l](3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof and a second drug which

is an inhibitor, inducer of substrate of P450 isoenzyme 3A4 of the kind such as herein described, with ratio percentages of first drug: second drug from

between 0.25:99.75% w/w and 99.5:0/5% w/w.

2. A non-interacting drug combination as claimed in claim 1, wherein the said second drug is an inhibitor or inducer of P450 isoenzyme 3A4.

3. A non-interacting drug combination as claimed in either claim 1 or claim 2, wherein each drug is administered together or each drug is administered

sequentially.

4. A non-interacting drug combination as claimed in any claim from 1 to 3, wherein the said second drug is used to lower cholesterol and is an inducer,

inhibitor or substrate of P450 isoenzyme 3A4.

5. A non-interacting drug combination as claimed in claim 4, wherein the said second drug is selected from bezafibrate, clofibrate, fenofibrate,

gemfibrozol and niacin.

6. A non-interacting drug combination, as claimed in claim 5, wherein the said second drug is fenofibrate.

7. A non-interacting drug combination, as claimed in any claim from 1 to 3, wherein the said second drug is used in treating cardiovascular conditions

and is also inhibitor, inducer or substrate of P450 isoenzyme 3A4.

8. A non-interacting drug combination as claimed in claim 7, wherein the said second drug is selected from digitoxin, diltiazem, losartan, nifedipine,

quinidine, verapamil and warfarin.

9. A non-interacting drug combination as claimed in any claim from 1 to 3

wherein the said second drug is used in immunosuppresion therapy and is an

inducer, inhibitor or substrate of P450 isoenzyme 3A4.

10. A non-interacting drug combination as claimed in claim 9, wherein the second drug is selected from cyclosporine, tacrolimus and a corticosteroid.

11. A non-interacting drug combination, as claimed in any claim from 1 to 10, wherein (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2[methyl (methylsulfony)

amino]pyrimidin-5-yl](3R, 5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof is dosed at 5, 10, 20, 40 or 80 mg once

per day.

12. A pharmaceutical formulation comprising a non-interacting drug combination as claimed in any of the preceding claims, wherein it comprises (E)-

7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl (methylsulfonyl) amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically

acceptable salt thereof, a drug which is an inducer, inhibitor or substrate of P450 isoenzyme 3A4 and a pharmaceutically acceptable diluent, carrier or

adjuvant of the kind such as herein described.

13. A pharmaceutical formulation, as claimed in claim 12, wherein the said second drug is a substarate of P450 isoenzyme 3A4 and is selected from

acetaminophen, aldrin, aflentanil, amiodorane, astemizole, benzphetamine, budenoside, carbamazepine, cyclophosphamide, cyciosporin, dapsone,

digitoxin, ditiazem, diazepam, erthrornycin, etooposide, flutamide, hydroxyarginine, ifosphamide, imipramine, lansoprazole, lidocaine, lovatidine, losartan,

lovastatin, midrazolam, nifedipine, omeprazole, quinidine, rapamycin, retinoic acid, steroids, tacrolimus, teniposide, theophyline, toremifene, triazolam,

troleandomycin, verapamil, warfarin, zatosetron and zonisamide.

14. A pharmaceutical formulation as climed in claim 12, wherein the said second drug is an inhibitor of P450 isoenzyme 3A4 and is selected from

clotrimazole, ethinylestradiol, gestodene, itraconazole, ketoconazole, miconazole, diltiazem, naringenin, erythromycin, cyclosporine and

triacetyloleandomycin.

15. A pharmaceutical formulation as claomed in claim 12, wherein the said second drug is an inducer of P450 isoenzyme 3A4 is selected

arbamazepine, dexamethasone, Phenobarbital, phenytoin, rifampin, sulfadimidine, sulfinipyrazone and triacetyloleandomycin.

16. A pharmacy pack whenever comprises the non-interacting drug combination as claimed in any of the preceding claim, comprising the first drug

which is (E)-7-[4-)4-fluorophenyl)-6-isopropyl-2-[methyl (methylsulfonyl) amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid or a

pharmaceutically acceptable salt thereof and the second drug which is an inducer, inhibitor or substrate of P450 isoenzyme 4A4.

The invention concerns safe non-interacting drug combinations of a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, which is

(E)-7-[4-(4-fluorophenyl)6-isopropyl-2-[methyl (methylsulfonyl) amino]pyrimidin-5-y l](3R, 5S)-3-5- dihydroxyhept-6-enoic acid or a pharmaceutically

acceptable salt thereof (the agent) and a drug which is either an inducer, inhibitor or a substrate of cyctochrome P450, in particular cytochrome P450

isoenzyme 3A4. Particular combinations are useful in treating hyperlipidaemia in humans who are receiving immunosuppressive chemotherapy. A

preferred combination is the agent and a fibrate drug, the use of such a combination in treating hyperlipidaemia in mammals, and medicaments

containing such a combination for use in such treatments.

7. The learned counsel for the appellant submitted that at the time of the invention lovastatin was the most successful statin. Rosuvastatin was not an

invention nor was substrate 3A4. This invention is only a combination of the two. He referred to the complete specifications and submitted that if it is

a non-interacting drug combination then there was no synergy and no patent can be granted. He also submitted that reductase inhibitor are admittedly

prescription drugs.

8. The learned counsel submitted that the dosage was no invention. He submitted that the stand of the respondent that through the use of the agent in

clinical study it was found that the agent may be conveniently dosed to patient was only standard routine experiment. He also submitted that when the

specification itself talks of agents it means more than one agent. No invention can be claimed alleging that they had combined the supersatin for the

first time.

He also submitted that the assessment does has not give the results and though the patentee claims to have stated the assessment data no results are

given. Labour cannot be awarded with a patent. It can be granted only for

technical advancement. The learned counsel submitted that there was no

prior art which clearly covers the drug so there was no anticipation. But the invention was obvious. He submitted that the invention was a non-

interacting drug combination of rosuvastatin and inhibitor inducer or substrate of P450 enzymes 3A4. The prior art '471 discloses and claims

Rosuvastatin and states that the compounds of the present invention inhibit the HMG-CoA reductase and subsequently suppress the piosynthesis of

cholesterol and they are useful in the treatment of hypercholeslerolemia, hyperlipoproteinemia and atherosclerosis (Abstract) The learned counsel

submitted that it was well known that statins lowers the plasma concentration. The statins are useful in treatment of hyperlipidemia. The combination

of two drugs was also well known. Exhibit 4 shows that lovastatin and simvastatin should not be used constantly with CYP3A4. Therefore a non-

interacting drug combination of CYP3A4 inhibitor with a satin non metabolized by CYP3A4 was obvious. He referred to various prior arts to show

obviousness. This was the only ground urged by him to show obviousness.

9. The learned counsel for the respondent submitted that though '471 deals with rosuvastatin, this combination was not taught. The adverse side-

effects of statin fibrate combination therapy actually discouraged this combination. In any event this is a super statin. The only other current

superstatin on that date was atorvastatin. No prior art encourages the person skilled in the art to try rosuvastatin in combination. It was the

respondent's invention which combined the two to advantage since rosuvastatin was not metabolised and there was very little clinical interaction. She

prayed that the appeal be dismissed.

Exhibit 2 is EP 0521 471 ('471 in short) is an invention of ""pyrimidine derivatives as HMG-CoA reductase inhibitors. Admittedly it deals with

rosuvastatin. This is acknowledged as a prior art in the patent specifications.

Exhibit 3 is ""Long term efficacy and safety of fenofibrate and a statin in the treatment of combined hyperlipidemia"" by L.B. Ruth et al. This says that

while combination therapy with gemfibrozil and lovastatin is effective in reducing tryglicerides and LDL cholesterol but experience in such therapy is

limited because of risk of myopathy and other severe complications. This prior art discloses the result of trials of combination fibrate/statin therapy. It

reports over all decrease in cholesterol but notes that clinicians may be reluctant

to use fibrate/statin combination therapy due to rare but potentially

severe myopathic complications. This prior art ends on a cautious note.

Exhibit 4 is ""Different effects of itraconazole on the pharamacokinetics of fluvasatin and lovastatin"" by K.T. Kivisto et. al. It is a study to ""evaluate the

hypothesis that fluvastatin is less liable to interaction with CYP 3A4 inhibitors than lovastatin. ""In conclusion, Lovastatin (and simvastatin) should not

be used concomitantly with potent CYP 3A4 inhibitors or the dosage of these statins should be greatly reduced while using CYP3A4 inhibitors"" and

that fluvastatin had much less potential for clinically significant interactions.

Exhibit 5 is ""Synthesis and biological Activity of methanosulfaonamide Pyrimidine -and N-Methanesulfonyl Pyrrol-Sunstituted 3,5 Dihydroxy-6-

heptenoates, a Novel Series of HMG-CoA Reductase Inhibitors"" by Watanabe et al. This speaks of rosuvastatin, and that it has greater enzyme

inhibitory activity than lovastatin and pravastatin. It was found to be approximately 100 times more potent than pravastatin. ""They are promising

candidates for development of anti arterosclerotic agents

Exhibit 6 is EP 0475 148 - ""Pravastatin alone or in combination with a fibric acid derivative for preventing onset or treating type III

hyperlipoprotaemia"". This says that CYP 3A4 is responsible for the metabolism of the widest range of drugs. It acknowledges that there is risk of

cardiotoxic drug interactions and that one mode to avoid it is prescription of alternative agents. This is shown in table 2 where 5 statins are mentioned.

Exhibit 7 is ""Update clinically significant cytochrome P450 drug interactions - Elizabeth Landrum Michalets (1998). It studied substrates inhibitors and

inducers of CYP 450 isoenzymes because that knowledge would help in predicting clinically significant drug interactions.

10. The expert Dr. Peeyush Jain is of the opinion that it is obvious that

10. The fact that combination of statins was generally considered safe is further supported by a later published article Jones et al (Reporting Rate of

Rhabdomyolysis with Fenofibrate + Statin Versus Gemfibrozil + Any statin, The American Journal of Cardiology, Vol. 95, Jan 1, 2005). It gives in

table 1, the number of prescriptions for each fibrate and statin dispensed between Jan. 1, 1998 and mar. 31, 2002). The number of reports of

Rhabdomyolysis for Fibrate and statin other than cerivastatin was found to be 0.58 case reported per million prescriptions.

15. This is further supported by a later published article, Evans et al.

(The myotoxicity of statins, Current opinion in Lipidology, 2002, 13, 415-420). It states that the difference in myotoxicity of different statins is not only

due to Pharmacokinetic properties but also depends on physicochemical and pharmacodynamic properties of individual drugs.

17. Moreover the assertions by the patentee, that there are no interactions between Rosuvastatin and cytochrome P450 3A4

inducer/inhibitor/substrate do not match with the data available as of date. The approved label of Rosuvastatin as mentioned below, has contradictions

related to some of the cytochrome P450 3A4 inducer/inhibitor/substrate.

21. In the absence of any data supporting the synergism between the two drugs, it should be considered as a mere combination of two drugs.

Feno fibrate plus simvastatin therapy...."" Wierzbicki et. al speaks of the combination therapy and that fibrate-statin was superior in all respects and

without any significant side effects.

11. ""Clinical Pharmacokinetics of Fibric Acid Derivatives"" by Miller et al:- This says that Fibrates are metabolised by hepatic cytochromes P450

(CYP)3A4 one of the reason for drug interactions with fibrates is that P450 CYP 3A4 is required for metabolism of all members of this class of

drugs. It says that combination of a statin and fibrate have made the combination of these two classes of drugs both clinically attractive and

problematic.

12. Evans et al ""The myotoxicity of statins"" says that the statins particularly the first generation statins have been well evaluated for safety and

efficacy. ""Cerivastatin was associated with 10 fold higher incidence of myotoxicity than any other statin, suggesting that there may be differences in

myotoxic potential between agents."" Cerivastatin was later withdrawn. This study says that the choice of hypolypidemic therapy needs to be based not

only on outcome evidence and cost-effectiveness analysis.

13. What do the patent specifications say?

It tells us that this invention is safe and non-interacting. It is a combination of the Agent (explained in the specification) and a fibrate drug (also

explained). The first generation statins are derivatives of fungal metabolites and the second generation ""superstatins"" are synthetic. The Agent is

rosuvastatin and is a superstatin. Atorvastatin also a super statin has been successful over the first generation statins. It was launched in 1997 and the

sales doubled in 1998, It is the most widely prescribed hypolipidaemic agent in the US. Despite the impressive benefits of statin therapy, it may result

in less than optimal therapeutic results, probably because of reversible increases in liver transminase levels. And that Clinically important elevations in

serum alanine aminotransferase have been reported for atorvastatin in 0.8 percent of patients. And it is the incidence of ALT increases which limits

dose escalations of statins. Superstatins lower cholesterol levels to a much higher degree than the statins before their does is limited by statin levels.

An additional adverse event is myopathy. Insevere cases it may lead to rhabdomyolysis. Myopathy and rhabdomyolysis have been particularly

associated with taking a statin in combination with P450 isoenzyme3A4. Therefore on the date of the invention on the labels of all commercially

available statins, the use of the statins in combination with drugs that are metabolised by P450 3A4 is not recommended.

14. The liver is the major site of drug metabolism and cytochrome represents a major class of drug metabolising enzymes. The specifications says that

the major disadvantage with the ""currently available superstatin, atorvastatin is that it is metabolised by cytochrome enzymesP450 enzymes. All the

first generation statins are also metabolised by P450. So though pravastatin has lower efficacy, it is the statin of choice ""in combination with other

drugs where the possibility of drug interactions is unacceptably high.

15. It specifically states that rosuvastatin is not metabolised by cytochrome P450 3A4 and does not possess the same potential for drug interaction as

the other superstatin which is currently available i.e. atorvastatin nor the other statins. Therefore they say that their invention is a non-interacting drug

combination comprising rosuvastatin and the cytochrome.

16. The specification says ""Therefore the possibility of combining the Agent, which is not metabolised by P450 3A4, with a fibrate and an

immunosuppressive therapy offers the additional possibility of lowering cholesterol to a greater extent in such patients than previously achieved and

more safely than could previously be achieved by the administration of a statin, a fibrate and an immunosuppressive drug. Fibrate drugs are thought to

act through peroxisomal proliferating activator receptor-a (PPAR-a) and affect

gene activation at a number of genes involved in atheroma. Patients

on fibrate drugs show improved LDL subfraction distribution (reduced VLDL and raised HDL), reduced LDL and reduced triglyceride levels, and

possible advantages through improving insulin sensivity. Examples of fibrate drugs include, bezafibrate, ciprofibrate, fenofibrate and gemfibrozol. By

use of the term 'safe non-interacting statin therapy' we mean that the agent is not metabolised by P450 3A4 and therefore does not affect the

metabolism of the immunosuppressive therapy or vice versa"" and ""Myopathy and rhabdomyolysis have been associated with taking a statin in

combination with gemfibrozil, niacin, cyclosporine or erythromycin, (HMG CoA reductase inhibitors, Hunninghake, Current Opinion in Lipidology

(1992) 3, 22-28) which are also substrates for P450 3A4. Additionally, adverse events associated with taking a fibrate drug have also been reported to

increase with concomitant statin therapy, such as a myosistis-flu like syndrome, which occasionally occurs in patents receiving gemfibrozil, increases

to 5% of patients when a statin is also administered. Combination of a statin with a fibrate drug is contraindicated on the labels, both in the USA and

Europe, of all commercially available statins. Despite the possibility of the occurrence of serious drug interactions doctors do prescribe combination

therapy of a statin and a fibrate drug to patients with more severe levels of hypercholesterolaemia, such as in patients with familial combined

hyperlipidaemia where the risk of a serious drug interaction is outweighed by the benefits of the combination therapy.

17. We have already extracted the evidence of Dr. Peeyush Jain, the appellant's expert. In this regard, the following paragraphs are also useful:-

4. As I understand the crux of the invention lies in finding out metabolic pathway of Rosuvastatin and combining it with other drugs which have a

different metabolic pathway. For a pharmacologist, it is a matter of routine experimentation to determine metabolic pathway of a drug as accepted by

the Patentee in the specification at page 6, line 5 onwards, Whether a drug is an inhibitor, inducer or substrate of a P450 enzyme can be easily

determined by procedures known to the skilled person. Such procedures may involve the exposure of a radiolabelled drug to hepatocytes or

hepatocyte microsomes or isolated P450 enzyme and the use of analytic techniques, such as HPLC, in determining metabolite formation.

After the metabolic pathway of drug is known, a skilled person would be able to combine it with drugs which are metabolized by different enzymes, so

as to obtain a non interacting combination.

5. As disclosed in Miller et al. (Clinical Pharmacokinetics of Fibric Acid Deriatives (Fibrate), 1998, 34 (2), 155-162), it is advisable to avoid a drug

which is a cytochrome P450 3A4 inducer/inhibitor/substrate with a fibrate,

The second principal cause of drug interactions with fibrates is that cytochrome P450 3A4 is required for metabolism of all members of this class of

drugs. Any drug, or other chemical, that modifies the activity of CYP 3A4 or itself requires CYP 3A4 for its metabolism can be affected by the

simultaneious administration of a fibrate.

In view of this statement, a skilled person after knowing that Rosuvastatin is not metabolized by CYP 3A4, would have combined it with fenofibrate or

other cytochrome P450 3A4 inducer/inhibitor/substrate.

18. He has discussed Fehrer et al, and Wierzbicki et. al, He has relied on a 2005 article which shows combination of statins was considered safe.

19. This is further supported by Miller et al. which states that though there have been reports for interaction between statins and fibrates combination

but the incidence is as low as 1%.

However, in a review of all reported clinical trials involving the combination of an HMG-CoA reductase inhibitor and a fibrate, Shepherd estimated the

rate of myopathic complications at 1% (5 cases amongst 516 pateitns). None of these 5 cases was of a severe nature. Shepherd clearly points out the

different conclusion that can be drawn from a meta analysis of clinical trials (1995) versus the post-marketing surveillance and adverse drug reaction

data.

20. Furthermore, the patentee has given the only reason for myopathy as CYP 3A4 interaction. This is contradictory to the known facts. As given in

Miller et al.

The exact mechanism underlying this drug interaction and the subsequent myotoxicity is unknown. Members of both classes of drugs have been

reported to cause myotoxicity when used as monotherapy. Both classes of drugs require CYP 3A4 for their metabolism and, therefore, could delay

metabolism of the other. However, I study has shown no difference in the

pharmacokinetics of fluvastatin and gemfibrozil whether they are

administered alone or together

Evans et al which he has relied on is a post grant document.

21. ""This could be the reason, though Rosuvastatin is not metabolized by CYP 3A4, but still interactions with cytochrome P450 3A4

inducer/inhibitor/substrate is observed, as given in more detail below.

22. ""Further, there have been reports of severe clinical interaction between Rosuvastatin and fenofibrate as given in Dedhia et al. (Journal of

Association of Physicians of India, 2007, Vol. 55, page 152-153). As disclosed in the article, the interaction was to an extent that combination therapy

of Rosuvastatin and Fenofibrate was discontinued and was replaced with combination of Rosuvastatin and ezetimibe,

23. This evidence is largely based on post-grant documents. Therefore that portion of the evidence cannot be accepted. The Inventor's case is that on

the date of the invention the only currently popular super statin was atorvastatin. It was metabolised by the cytochrome. This invention is in the non-

interacting combination of rosuvastatin with a cytochrome. Rosuvastatin is minimally metabolised by the cytochrome.

24. The expert's affidavit does not address this. The Inventor's case is that when there were many safety issues with the statin-fibrate combination

therapy, and when the currently popular super statin was metabolised by the cytochrome, the person skilled in the art is not likely to try the super

statin. Further the expert says that the crux of the invention is finding the metabolic pathway of Rosuvastatin and combining it with other drugs having

different pathways. Then he says that for a person skilled in the art this is a matter of routine experimentation. That means though it is not known it

can be found by routine experimentation. That is, it may be novel but it is obvious. On the other hand the applicant says that Ex. 2 is rosuvastatin and

non-metabolisation is inherent in Ex. 2. That means it is an inherent quality of a known object. But curiously the expert says that after knowing that it

is not metabolised the person skilled in the art would have combined rosuvastatin with fibrate since Miller et al says that a drug which is metabolised

by a fibrate can be affected by simultaneous administration of a fibrate. Therefore he says that this is only a discovery and not an invention. The

expert says that the patentee's assertion that it is a non-interacting combination

has been proved false by post grant literature.

25. The expert has not addressed the argument advanced by the Patentee in favour of non-obviousness. Post transplant patients receiving immuno

therapy may be susceptible to accelerated atherosclerosis, since certain immune suppressive drugs raise the levels of fibrinogen and lipoprotein in

patients. According to the specifications, it was known that statins lower cholesterol levels, and of the statins, pravastatin was the drug of choice since

it had a lower incidence of serious drug interaction with the immunosuppressive therapy. Atorvastatin was metabolised by the fibrate. Atorvastatin

was the current superstatin at the time of the invention. Though rosuvastatin was known, the Patentee says there was no indication to teaching in the

prior art for the person skilled in the art to try experimenting with rosuvastatin.

26. The Appellant relied on the relevant paragraphs in Laboratories Almirall vs Boehringer Ingelheim International GmBh in Claim No HC 07 C0 2104

the Chancery court's judgment which refers to combination therapy and Speculative patents and ex-post facto justification. The court says that the

sufficient justification for the solution must be found in the patent as filed.

27. The patentee has referred to the difficulties faced by post transplant patients receiving immuno-suppressive therapy. It has referred to the

discouragement in the prior art teachings regarding statin-fibrate therapy. It has also referred to the problems in using atorvastatin. It claims that since

rosuvastatin is very minimally metabolised by the cytochrome, the proportion in which it is combined makes it a non-interacting drug. So the

specifications make it clear why they claim a patent.

28. Ex. 3 which is a 1998 document shows that on that date the ""experience in the use of combined fibrate-statin therapy has been limited"" because

the earlier reports suggested risk of myopathy with severe complications. So they studied the efficacy and safety of fenofibrate with a low dose of

pravastatin and simvastatin. It is a cautious study and while the tests reported low incidence of side-effects, it is noted that this may be due to low

dosage of statin employed in combination therapy. It also notes that there is a small but significant increase in serum creatinine both in fenofibrate

monotherapy and in combination therapy. So the state of the art appears to have been cautious and not adventurous.

29. Ex. 4 is about fluvastatin and lovastatin, and so cannot really teach the

invention, on the contrary it says that these two statins should not be used

concomitantly with CYP 3A4 inhibitors, or if they are they should be greatly reduced.

30. Ex. 5 is Watanabe et al which was relied on by the Opposition board to hold against the inventor. Watanabe reports that Rosuvastatin possesses

greater enzyme inhibitory activity than lovastatin and pravastatin. It also indicates that experiments are in progress and that this is a promising

candidate for development of anti arterosclerotic agents. This was in 1997. Ex. 3 also reflects the position in 1997, though it was accepted in 1998. Ex.

7 (1998) refers to the explosion of information of cytochrome enzymes, and that knowledge of the substrates and inhibitors of these enzymes assist in

predicting clinical interactions. In this study (Table 2) the statins that have been employed do not include Rosuvastatin, though the other superstatin viz:

atorvastatin has been used. The Management of the drug indicates that the administration must be monitored for myopathy. This study reads thus:"" As

mentioned HMG CoA reductase inhibitors are metabolised by the 3A4 system and have dose-related toxic effects on skeletal muscle that may range

from diffuse myalgia and myopathy to severe rhabdomyolysis. These effects are reported most frequently with lovastatin but have also been reported

rarely with the other statins. The risk of rhabdomyolysis appears to be the greatest when HMG CoA reductase inhibitors are combined with 3A4

inhibitor drugs or agents that compete with 3A4 metabolism."" So on that date the person skilled in the art looked at statins as being metabolised by the

3A4 system and as posing risk of side effects.

31. Ex. 8 relates to Lescol tablets (Novartis) which is fluvastatin sodium tablets. It shows that fluvastatin is metabolised by the liver.

32. Miller et al (1998) mentions the drug interactions with lovastatin, simvastatin, pravastatin and fluvastatin). It says that the principal cause of drug

interaction with fibrate is that Cytochrome P450 is required for the metabolism of all the members of this class of drugs, and that such drugs which are

metabolised can be affected by the simultaneous administration of a fibrate. This is a clear discouragement contrary to what the expert says.

33. The extract from this document above document is:-

The exact mechanism underlying this drug interaction and the subsequent myotoxicity is unknown. Members of both classes of drugs have been

reported to cause myotoxicity when used as monotherapy. Both classes of drugs require CYP 3A4 for their metabolism and therefore could delay

metabolism of the other. However, I study has shown no differe in the pharmacokinetics of fluvastatin or gemfibrozil whether they are administered

alone or together.

It is likely that differences among HMG-CoA reductase inhibitors, with respect to the potential for interactions with fibrates, ay be importantly

affected by bioavailability. We speculate that lovastatin, with a bioavailability of only 5%, and simvastatin, which also has a low bioavailability, may be

more affected by interactions with grapefruit juice and mibefradil than drugs that are not primarily metaboised by CYP 3A4, such as fluvastatin and

pravastatin. On the other hand, fibrates, as they are highly bioavailable, are unlikely to be affected by grapefruit juice, since the important interactions

with that food are limited to drugs which have low bioavailability due to first pass metabolism in the gut wall. Therefore, the important situation for

grapefruit juice in the context of fibrates, is in the patient receiving combination treatment with fibrate with statin drugs.

At present, the relative myotoxicity of each of the fibrates alone or in combination with an HMG CoA reductase inhibitor is unknown.

34. This was the knowledge that was available on the date of the invention. "". In the words found in Roche v. Cipla this person is a skilled worker in

the field concerned, with the state of knowledge existing at the date of the patent to be found in the literature then available. What was the knowledge

with which this person worked?

a) The myotixicity of each fibrate alone or in combination with statins was not known.

b) Statins were known to be metabolised by CYP 3A4 and as posing side effects.

c) In 1998, when there was an explosion of information in the arts, a study on clinical interactions seen in Ex. 7, statins were used but not rosuvastatin.

d) The state of the art was cautions because of the severe side effects.

e) As regards dosage even in other statin-fibrate combination therapy, it was modulated carefully.

f) Adverse events were reported with fibrate drugs when used in concomitant statin therapy.

g) Atorvastatin was the current favoured superstatin. It was metabolised.

h) In statin-fibrate combination therapy, drug interaction was high.

35. In this situation, the Person Skilled in The Art would not have been taught by the prior arts to experiment with a rosuvastatin-fibrate combination.

The Controller was right in his conclusion that it was non-obvious. This was the only ground raised. It is the respondent's case that by this particular

claimed drug combination there is no clinical interaction, which shows that it is not just a 1 +1 combination. We see no reason to interfere with the

impugned order.

36. The Controllers have to remember in Opposition proceedings, that they must deal with the Opposition Board's recommendations in their orders.

They are free to agree or to disagree, but it is a crucial part of the records before the Controller. If they are accepting the recommendations, perhaps

they need not deal with it at length. But when they disagree with it, as in this case, they must explain why and give reasons. In the result, we confirm

the decision of the Controller. The appeal is dismissed. No costs.

