ATORVASTATIN PATENTS

CLAIM CONSTRUCTION ANALYSIS

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What is Atorvastatin?

• One of a class of anti-cholesterol drugs known as statins
• Sold exclusively by Pfizer under the brand name Lipitor
  - Garnered over US $12B/yr in sales in 2006 and 2007
  - Pfizer has Five Patents Listed in the Orange Book for Lipitor
  - Ranbaxy Filed an ANDA and Was Then Sued by Pfizer
    • Only Involves Two Oldest Orange Book Patents
    • Appeals Court Ruled in Favor of Pfizer on One Patent
• Pfizer Sued Websites Over Fourth Orange Book Patent
Family Trees

06/868,867 (May 30, 1986)  
4,681,893 (Jul. 21, 1987)

07/384,187 (Jul. 21, 1989)  
Abandoned (Mar. 21, 1991)

07/660,976 (Feb. 26, 1991)  
5,273,995 (Dec. 28, 1993)

08/005,708 (Jan. 19, 1993)  
Abandoned (Aug. 5, 1994)

08/246,919 (May 20, 1994)  
5,686,104 (Nov. 11, 1997)

08/886,982 (Jul. 02, 1997)  
6,126,971 (Oct. 03, 2000)

60/001,452 (Jul. 17, 1995)  
Provisional (Jul. 17, 1996)

PCT/US96/11368 (Jul. 8, 1996)  
§371

08/945,812 (Oct. 2, 1997)  
5,969,156 (Oct. 19, 1999)
The '893 Patent

- 9 Claims, Only 1 Independent
- Claim 1: A compound of structural formula I

wherein [elemental specifications].

- “No intrinsic evidence limits to trans-racemates, as opposed to enantiomers or any (equal or unequal) mixtures thereof.” Pfizer v. Ranbaxy, 457 F.3d 1284 (Fed. Cir. 2006).
The '995 Patent

• Background

Trans- (+-)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamides are among compounds of U.S. Pat. No. 4,681,893 having usefulness as inhibitors of cholesterol biosynthesis. The compounds therein broadly include 4-hydroxypyran-2-ones and the corresponding ring-opened acids derived therefrom.

It is now unexpectedly found that the enantiomer having the R form of the ring-opened acid of trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-tetrahydro-4- hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide; that is [R-(R*,R*)]-2-(4-fluorophenyl).beta.,.delta.-dihydroxy-5-(1-methylethyl)- 3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, provides surprising inhibition of the biosynthesis of cholesterol.
The '995 Patent

• 12 Claims, Only 1 Independent:

1. \([R-(R^*,R^*)]-2-(4\text{-fluorophenyl})\cdot\beta\cdot\delta\cdot\text{dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid or (2R-trans)-5-(4\text{-fluorophenyl})-2-(1\text{-methylethyl})-N,4\text{-diphenyl-1-[2-(tetrahydro-4\text{-hydroxy-6-oxo-2H-pyran-2-yl})ethyl]-1H-pyrrole-3-carboxamide; or pharmaceutically acceptable salts thereof.}
The '104 and '971 Patents

- Background

CI-981 Hemi-Calcium is currently under development for the treatment of moderate to severe familial or nonfamilial hypercholesterolemia. The specific isomer (CI-981) has been described in U.S. Pat. No. 5,273,995. However, these compounds are unstable in that they are susceptible to heat, moisture, low pH environment, and light. When packaged in the form of tablets, powders, granules, or within capsules, the compounds may be further destabilized by contact with the molecular moieties of other components.

It is an object of the present invention to provide a stable solid peroral pharmaceutical formulation comprising substituted pyrrolyl substituted pyran ring-opened hydroxy acids for therapy of hypercholesterolemia or hyperlipidemia. More particularly, it is the object of the present invention to provide a stable solid peroral pharmaceutical formulation comprising a HMG CoA reductase inhibitor, such as the aforesdescribed CI-981 Hemi-Calcium, as active ingredient.
The '104 and '971 Patents

- 41 Total Claims, 11 Independents

'104 Patent, Claim 1. A pharmaceutical composition for the peroral treatment of hypercholesterolemia or hyperlipidemia characterized by improved stability comprising in a mixture, a compound as active ingredient of structural formula I

wherein [elemental specifications including a “stabilizing additive”].
The '156 Patent

• Background

The processes in the above United States Patents (the '893 and '995 patents) disclose amorphous atorvastatin which has unsuitable filtration and drying characteristics for large-scale production and must be protected from heat, light, oxygen, and moisture.

We have now surprisingly and unexpectedly found that atorvastatin can be prepared in crystalline form. Thus, the present invention provides atorvastatin in new crystalline forms designated Form I, Form II, and Form IV.
The present invention relates to novel crystalline forms of atorvastatin which is known by the chemical name \([R-(R^*,R^*)]-2-(4\text{-fluorophenyl})-\beta.,\delta.-dihydroxy-5-(1\text{-methylethyl})-3\text{-phenyl-}4-[(\text{phenylamino})\text{carbonyl}]-1\text{H-pyrrole-1-heptanoic acid hemi calcium salt.}

Forms I, II, or Form IV atorvastatin were characterized by their X-ray powder diffraction pattern. ... Table 1 lists the 2.\text{theta.}, d-spacings, and relative intensities of all lines in the unground sample with a relative intensity of >20% for crystalline Form I atorvastatin. ... Table 4 shows the solid-state NMR spectrum for crystalline Form I atorvastatin.
 Claims 1 – 5: A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing [some specified] $2\theta$ values measured using CuK$\alpha$ radiation.

 Claims 6 – 9: A crystalline Form I atorvastatin hydrate characterized by solid state $^{13}$C nuclear magnetic resonance having [some specified values] chemical shift [characteristics].

Choosing Which Claims To Analyze

• Which Patent
  – '893 & '995 Patents Challenged in Ranbaxy Litigation
  – '104 and '971 Patents Not Asserted by Pfizer
  – '156 Patent Asserted Against Websites and Not Otherwise Being Challenged

• Which Claims of '156 Patent
  – Claims 1-9 are Each Independent and Directed to Form I
Prosecution History of '156 Patent (1)

- Jul. 17, 1995: Provisional Application Filed w/ 29 Claims
- Jul. 8, 1996: PCT Application Filed
- Oct. 2, 1997: National Stage Election; Preliminary Amendment

“[T]he subject invention defines three novel crystalline Forms – Forms I, II and IV – of the compound atorvastatin. … [E]ach of the crystalline forms is the same in that each consists of the atorvastatin compound described above. However, each of the crystalline forms is different from the other crystalline forms in that each has a different x-ray powder diffraction or solid state $^{13}$C magnetic resonance identifying characteristic.”

“[T]he crystalline forms of atorvastatin are distinguished from the amorphous form of atorvastatin because the amorphous form does not have any distinct x-ray powder diffraction lines.”
Prosecution History of '156 Patent (2)

- Jun. 6, 1998: Office Action
  - 102(b) Rejection: “Bocan et al. disclose atorvastatin which may be in crystalline or amorphous form.”
  - 103 Rejection: “The claims differ from the teachings of Bocan et al. because they claim a specific crystalline form of atorvastatin. It would have been obvious ... to crystallize the atorvastatin taught by Bocan et al. to make the invention of the applicants.”
Prosecution History of '156 Patent (3)

• Dec. 3-4, 1998: Interview by Telephone

Description of the general nature of what was agreed to if an agreement was reached, or any other comments:
Agreement was reached that the applicants would submit raw data to support any claim of unexpected results. The examiner informed the applicant's attorneys that bioavailability must be disclosed in the specification as a critical feature of the invention in order for it to be relied upon to distinguish over the teachings of the prior art on the basis of unexpected results. The applicants' test data was discussed.
Prosecution History of '156 Patent (4)

• Dec. 9, 1998: Amendment
  - 102(b) Rejection: Argues Bocan et al. did not disclose crystalline Forms I, II or IV and supports with declarations.
  - 103 Rejection: “It is well known that a crystalline form of a pharmaceutical agent would be expected to have poorer bioavailability compared to an amorphous form. [Cites reference.] ... It was both surprising and unexpected that a crystalline form of atorvastatin has good bioavailability.” Supports with declaration.

• Feb. 4, 1999: Notice of Allowance
  - “Applicant's declarations are found persuasive because they distinguish the claimed compounds from those of Bocan et al..”
Claim Construction of The '156 Patent

• Claims 1-9: “A crystalline Form I atorvastatin hydrate:
  (a) having an X-ray powder diffraction containing [some specified] 2θ values measured using CuKα radiation; or
  (b) characterized by solid state ¹³C nuclear magnetic resonance having [some specified values] chemical shift [characteristics].

• “Atorvastatin” defined by spec as “known by the chemical name [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt.” 1:13-16.
Reference Searching

• Searches Performed; Relevant References Identified
  - All Related Families
    • '893 Patent: Atorvastatin Compound
    • '995 Patent: Atorvastatin Enantiomers
    • '104 Patent: Stable Atorvastatin Formulations
  - Boolean terms: atorvastatin, crystalline, CI-981
    • No additional relevant references found.
  - Classification: 548/537
    • No additional relevant references found.
Prior Art Determinations

• '156 Patent Effective Application Date = Jul. 17, 1995

• Ref #1: '893 Patent
  – Issued Jul. 21, 1987 .: 102(b) Prior Art

• Ref # 2: '995 Patent
  – Issued Dec. 28, 1993 .: 102(b) Prior Art

• Ref # 3: '104 Patent
  – Effective Application Date Jan. 19, 1993 .: 102(e) Prior Art
Prior Art Application

• '995 Patent: Atorvastatin Enantiomers

  “EXAMPLE 10
  Calcium Salt from Sodium Salt and/or Lactone ...
  Can be recrystallized.”

• '104 Patent: Stable Atorvastatin Formulations

  “EXAMPLE A
  Calcium Salt from Sodium Salt and/or Lactone ...
  The product can be recrystallized ....”
Validity Arguments / Issues

• '995 Patent Discloses Crystalline Atorvastatin
  - Example 10 states the compound “Can be recrystallized.”
  - Unsure of characteristics of crystallized atorvastatin.

• '104 Patent Discloses Crystalline Atorvastatin
  - Example A states “The product can be recrystallized.”
  - Unsure of characteristics of crystallized atorvastatin.
Conclusions

1. Substantial questions regarding the validity of claims 1-9 of the '156 patent exist.

2. Namely, the '995 patent and '104 patent qualify as prior art to the '156 patent and seem to each disclose crystalline atorvastatin.

3. It is uncertain whether the prior art atorvastatin contains the characteristics claimed in the '156 patent.