Purpose of Paragraph IV Certifications and Notice Letters

- Background of Hatch-Waxman

  - Roche Products Inc. v. Bolar Pharmaceutical
    - 733 F.2d 858 (Fed. Cir. 1984)
    - Any testing work for FDA approval will infringe patent
    - Extends patent term
    - Results in delay of generic entry into market

    - Allows testing related to FDA approval 35 U.S.C. 271(e)(1)
    - Balances interests of Big Pharma and Generics
    - Incentive to challenge patents for early entry of generics
      (180 day exclusivity if successful challenge)
    - Protection of Brand Patents (automatic FDA 30 month stay of ANDA Approval)
Purpose of Paragraph IV Certifications and Notice Letters (continued)

- **Paragraph IV Certification**
  - Statutory Requirement of ANDA
  - Tells the FDA that the patent listed in the Orange Book is invalid or not infringed by the ANDA product

- **Orange Book Listings ("Listed Patents")**
  - Found on FDA Web Page (fda.gov)
  - NDA Owner (New Drug Application)
  - Multiple Patents
  - Includes Additional Notes and Information
    - New Chemical Entity Exclusivity
    - Pediatric Exclusivity
Electronic Orange Book
Approved Drug Products
with
Therapeutic Equivalence Evaluations
Current through July 2007™

** In order to provide timely consumer information on generic drugs, the Electronic Orange Book will be updated daily as new generic approvals occur. Refer to FAQ for additional information. [New!]

Annual Edition
FAQ

Search by Active Ingredient  Search by Applicant Holder

Search by Proprietary Name  Search by Application Number

Search by Patent

The products in this list have been approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

Drug questions email: DRUGINFO@CDER.FDA.GOV

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Science
Office of Generic Drugs
Electronic Orange Book Query

Search by Proprietary Name:

[Type in part or all of name]

Select the list you would like to search:

- Rx (Prescription Drug Products)
- OTC (Over-the-Counter Drug Products)
- Disc (Discontinued Drug Products)

[Submit] [Clear]

Return to the Electronic Orange Book Home Page
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Patent and Exclusivity Info for this product: View

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
- Orange Book Data - Monthly
- Orange Book Data Updated Through July, 2007
- Patent and Generic Drug Product Data Last Updated: August 17, 2007
**Patent Data**

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**Exclusivity Data**

There is no unexpired exclusivity for this product.

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(6).
2. Patents submitted on FDA Form 3542 and listed after August 18, 2003 will have one to three patent codes indicating specific patent claims as submitted by the sponsor and are detailed in the above. These patents may not be flagged with respect to other claims which.
3. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor.
4. "PED" and "PED" represent pediatric exclusivity. Patents with pediatric exclusivity granted after August 18, 2003 will be indicated with "*PED" as was done prior to August 18, 2003. Patents with "*PED" after August 18, 2003 will not contain any information relative to the patent itself other than the "*PED" extension. Information related specifically to the patent will be conveyed on the original patent only.
Exclusivity Data

There is no unexpired exclusivity for this product.

Additional information:

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3. Patents listed prior to August 19, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.
4. *PED and PEO represent pediatric exclusivity. Patents with pediatric exclusivity granted after August 19, 2003 will be indicated with *PED as was done prior to August 19, 2003. Patents with *PED added after August 19, 2003 will not contain any information relative to the patent itself other than the *PED extension. Information related specifically to the patent will be conveyed on the original patent only.
5. U.S. Patent Nos. RE 35491 and RE 36290 were related for Zocor (NDA 19-768) pursuant to the decision and related order in Ranbaxy Labs. v Leavitt, No. 05-1898 (D.D.C. April 30, 2008). The 481 and 520 patents remained listed in Approved Drug Products with Therapeutic Equivalence Evaluations until any applicable periods of exclusivity pursuant to section 505(b)(2)(B)(iv) of the Federal Food, Drug, and Cosmetic Act were triggered and run. For additional information on this matter, please refer to Docket Nos. 2005P-0005 and 2005P-0046. Patents were subsequently delisted in the December 2006 Orange Book update as the exclusivity periods have triggered and run to expiration.
Purpose of Paragraph IV Certifications and Notice Letters (continued)

- Types of Certification Letters to FDA
  
  
  - Paragraph I, No Listed Patent
  - Paragraph II, Patent has expired
  - Paragraph III, Will Wait for Patent to Expire
  - Paragraph IV, Patent Not Valid or Not Infringed
Combining Different Paragraphs in Single Certification

- Can Include Paragraph IV’s and Paragraph III’s in same Certification
  - Paragraph III for molecule patent
  - Paragraph IV for formulation patent
- Can Also Include “Section viii” Labeling Carve Out for Method of Treatment Patents
Purpose of Paragraph IV Certifications and Notice Letters (continued)

- **First, Certification is Sent to FDA**
  - Includes Statement Applicant Will Send Notice Letter, 355(j)(2)(B)(i)
  - Within 20 days of FDA receipt of new filing; or at time of any ANDA Amendment to Certification 355(j)(2)(B)(ii)
  - Notice Letter to each patent owner and holder of approved application (NDA), 355 (j)(2)(B)(iii)
    - Registered or Certified Mail Return Receipt requested
      - 21 C.F.R. 314.52(a)
      - Important Date for start of 30 month stay.
Purpose of Paragraph IV Certifications and Notice Letters (continued)

- NDA Holders listed in Orange Book
- Determining Patent Owners or Representative Designated to Receive Service Can Be Tricky
  - Start on Patent or recorded at USPTO
  - Ownership Not Always Recorded at PTO
    - Large Corporations Change Ownership
- Multiple patents can mean multiple patent owners
- Send to Anyone That You Think May Own Patent
United States Patent

Barnes et al.

Patent Number: 4,721,723
Date of Patent: Jan. 26, 1988

Inventors: Roger D. Barnes, Betchworth; Marian W. Wood-Kaczmar, Harlow; Alan D. Curzons, Worthing; Ian R. Lynch, Epsom; John E. Richardson, Harlow; Philip C. Buxton, Epsom, all of England

Assignee: Beecham Group p.Lc., Brentford, England

Appl. No.: 922,530
Filed: Oct. 23, 1986

Foreign Application Priority Data
Oct. 25, 1985 [GB] United Kingdom ................. 8526407
Oct. 25, 1985 [GB] United Kingdom ................. 8526408

Int. Cl.4 .................. A61K 31/445; C07D 405/12
U.S. Cl. ........................................ 514/321; 546/197
Field of Search ....................... 546/197; 514/321

References Cited
U.S. PATENT DOCUMENTS
4,007,196 2/1977 Christensen ...................... 546/197

OTHER PUBLICATIONS

Primary Examiner—Richard A. Schwartz
Attorney, Agent, or Firm—James F. Haley, Jr.; Alan M. Gordon

ABSTRACT
The invention provides crystalline paroxetine hydrochloride hemihydrate, processes for its preparation, compositions containing the same and its therapeutic use as an anti-depressant.

6 Claims, 3 Drawing Figures
Purpose of Paragraph IV Certifications and Notice Letters (continued)

- Second, Notice Letter Sent to NDA and Patent Owners Triggers Dates
  - 45 days for NDA and Patent Owner to Sue ANDA Applicant
  - If Lawsuit filed, Automatic 30 Month Stay on Final FDA Approval Starts Upon Receipt of Notice
    - Different Generics in same case likely to have different dates when stay expires
    - Judge can lengthen or shorten stay depending parties conduct
  - Stay ends 30 months or lawsuit is resolved
  - Once stay ends Generic can launch “at risk”
Purpose of Paragraph IV Certifications and Notice Letters (continued)

- Benefit 180-Day Exclusivity Period
  - First ANDA filer is entitled to 180-day exclusivity over subsequent ANDA filers
- Old Rule Triggering 180-day exclusivity
  - 1st Filer must begin marketing, or
  - Receive court “decision” of non-infringement or invalidity
  - Multiple exclusivities possible
    - Cross Exclusivities
    - Parking Problems
  - 2nd Filer 30 month stay over but blocked by 1st Filer’s 180 day exclusivity
Purpose of Paragraph IV Certifications and Notice Letters (continued)

- Benefit 180-Day Exclusivity Period (continued)
  - New Rule (“MMA Amendments”) to Address Problems (December 8, 2003) 1st Filer begins with marketing
    - Shared exclusivity for first filers
    - New Forfeiture provisions can trigger start of exclusivity
      - Failure to market after certain events (e.g. Court ruling, NDA withdrawal)
      - ANDA withdrawal
      - Change in patent certification, withdraw Para. IV
      - Failure to obtain tentative approval
    - “Authorized Generics” – Brand name re-packagers
      - Can sell during 180-day exclusivity period
Requirements and Strategies for Paragraph IV Certifications and Notice Letters

  - Paragraph IV Notice shall
    - (I) state application contains bioavailability or bioequivalence studies
    - (II) “include a detailed statement of the factual and legal basis of the opinion of the applicant that the patent is invalid or will not be infringed.”

- Where does this “opinion” come from?
- What is a “detailed statement”? 

Requirements and Strategies for Paragraph IV Certifications and Notice Letters (continued)

- Where does this “opinion” (detailed statement) come from?
  - Inside Attorneys
  - Outside Attorneys
  - API Suppliers
  - Should Come Early in Development Process

- Little Guidance on How Detailed is “Detailed Statement”
  - FDA and Courts have both punted
  - Must have some rational reasonable basis
    - Baseless non-infringement/invalidity position could be basis for “exceptional case” (attorney fees)
    - Typically reflects a patent opinion letter from a patent attorney
Requirements and Strategies for Paragraph IV Certifications and Notice Letters (continued)

- Non-Infringement
  - Patent claims determine infringement; each claim is important
  - Only need one missing limitation (Literal/DOE)
- Examples of Types of Patents
  - Composition/Molecule (API) (Listable)
  - Formulation (Listable)
  - Dosage Form (Listable)
  - Method of Treatment (Listable, Section viii carve out)
  - ONLY Compositions and Method of Treatments can be listed in the Orange Book
  - Method of Manufacture (Not Listable)
Requirements and Strategies for Paragraph IV Certifications and Notice Letters (continued)

- Invalidity/Unenforceability
  - Grounds for Invalidity/Unenforceability
    - Anticipation
    - Obviousness (no longer requires TSM test)
      - Reduces Showing Required by Generics
        - *Aventis v. Lupin, Ramipril* (Sept. 2007)
  - Enablement
  - Fraud on Patent Office
    - Burden on Generic to Prove invalidity/unenforceability
    - Strategically not as effective against other generic competitors
Requirements and Strategies for Paragraph IV Certifications and Notice Letters (continued)

- Strategies for “Detailed” Statement
  - Fewer Facts, Detail and Argument
    - May provoke lawsuit
    - Does not reveal litigation strategy
    - May only reveal strongest argument
    - Narrows potential discovery
    - Risk exceptional case finding- cannot be “wholly unjustified”
      Yamanouchi v. Darby 231 F.3d 1339 (Fed. Cir. 2000)
  - More Facts, Detail and Argument
    - May avoid lawsuit by showing strength of case
    - Needs to coincide with litigation strategy
    - Broadens potential discovery
Requirements and Strategies for Paragraph IV Certifications and Notice Letters (continued)

- **Offer of Confidential Access**
  
  - ANDA Applicant offers confidential access to application to allow evaluation for possible infringement
  - Separate document
    - Includes contract terms similar to those in a Protective Order
    - Limits persons entitled to access and use of information
    - Other terms: disposition of information, accidental disclosure, choice of law, signature confirmation of agreement to terms
  - Permits ANDA Applicant to file a Declaratory Judgment Action after 45 days, 355(j)(C)(i)(I)(cc)
    - Now even easier due to Caraco Pharma v. Forest Labs (Fed. Cir. April 1, 2008)
Effect of Certification and Notice Letters on Litigation

- Use of Certification and Notice Letters at Trial
  - Litigation arguments should be consistent with reasons for non-infringement and invalidity given in Notice Letter
    - Inconsistency can be evidence of bad faith
    - Can Result in Attorney Fees (Takeda v. Mylan $17 million)
  - Notice Letter can be Evidence of non-willfulness by showing due care and reasonable belief patent is not infringed or invalid
    - Narrows discovery issues and Waiver of attorney client privilege communications
    - Must have good faith belief of non-infringement/invalidity at time of filing ANDA
Effect of Certification and Notice Letters on Litigation (continued)

- **Difference Between Opinion Letters and Notice Letters**
  - Opinion Letters are sent between Attorney and Client and are protected by Attorney-Client Privilege
    - Not discoverable in litigation
    - Can include information sent by Inside Attorneys as well as Outside Attorneys
  - Notice Letters are not privileged communications and are subject to discovery
    - Notice Letters should be marked “Confidential” and include a confidentiality statement to protect information in “Detailed Statement” for being used for other purposes.
Effect of Certification and Notice Letters on Litigation (continued)

- Pre-Launch Litigation v. Post-Launch Litigation
  - Pre-Launch
    - Filing of ANDA with a Paragraph IV statement is act of infringement for jurisdictional purposes
    - No monetary damages
    - Relief is an injunction against FDA final approval and thus prevents sale of product
    - Send Notification Letter early to get 30 month stay clock ticking
  - Post-Launch
    - Commercial Litigation (make, use, sell, import, offer to sell)
    - “At Risk Launch” Monetary damages based on sales (trebled if willful infringement)
      - Lost Profits or Reasonable Royalty if sold during 180 days excl.
      - Injunction against continued making, using, selling
Strategies for Different Types of Patents

- Strategy Based on How Brand Acquires Patents and Manages Drug Lifecycle
  - Molecule/Composition (API)
    - Typically Paragraph III
    - Cannot avoid infringement by designing around patent
    - Paragraph IV only if invalidity or unforceability
  - Formulation
    - Typically Paragraph IV
    - Easier to design around to avoid infringement
      - Changing right excipients can be sufficient
    - Invalidity also available
Strategies for Different Types of Patents

- **Dosage Form**
  - Typically Paragraph IV
  - Usually narrow patent easy to avoid infringement
    - Patents cover specific combo/control products
    - Changing release mechanism avoids infringement
  - Usually strong invalidity arguments

- **Method of Treatment**
  - Can be easiest to avoid with simple labeling change
  - Section viii labeling “carve out” to remove reference to indication from labeling

- **Polymorph Patents** can be problematic if trace amounts
Strategies for Different Types of Patents

- **Brand strategies**
  - Include indication information in safety section of label
  - FDA will typically not allow labeling carve outs from safety section
  - Generic not permitted to remove language from label and thus could be found to induce infringement depending on market split on various indications
  - Brand does list all method of treatment patents in Orange Book
    - FDA will not permit section viii carve out on unlisted patents
- **Consider What Other Generics May Due**
  - Can they fight your battles or do you need the 180 days
Pepper . . . and Salt

THE WALL STREET JOURNAL

“We waited too long to run it by legal.
Now we need to run it by a judge.”
CONCLUSION

 Involve Lawyers Early in Drug Development Process and be confident in your non-infringement and invalidity positions prior to filing ANDA

 File and serve ANDA and Notification Letter as early as possible