St. Onge Steward Johnston & Reens LLC

STRATEGIES FOR FILING SUCCESSFUL PARAGRAPH IV CERTIFICATIONS

Presented at: **8th ANNUAL GENERIC DRUG SUMMIT**
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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
  - Hatch-Waxman Enacted (1984)
    - 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)
    - Protection of Brand Patents (automatic 30 month stay)

Purpose of Paragraph IV Certifications and Notice Letters (continued)

- Paragraph IV Certification
  - 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
  - NDA Owner
  - Multiple Patents
  - Includes Additional Notes and Information

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

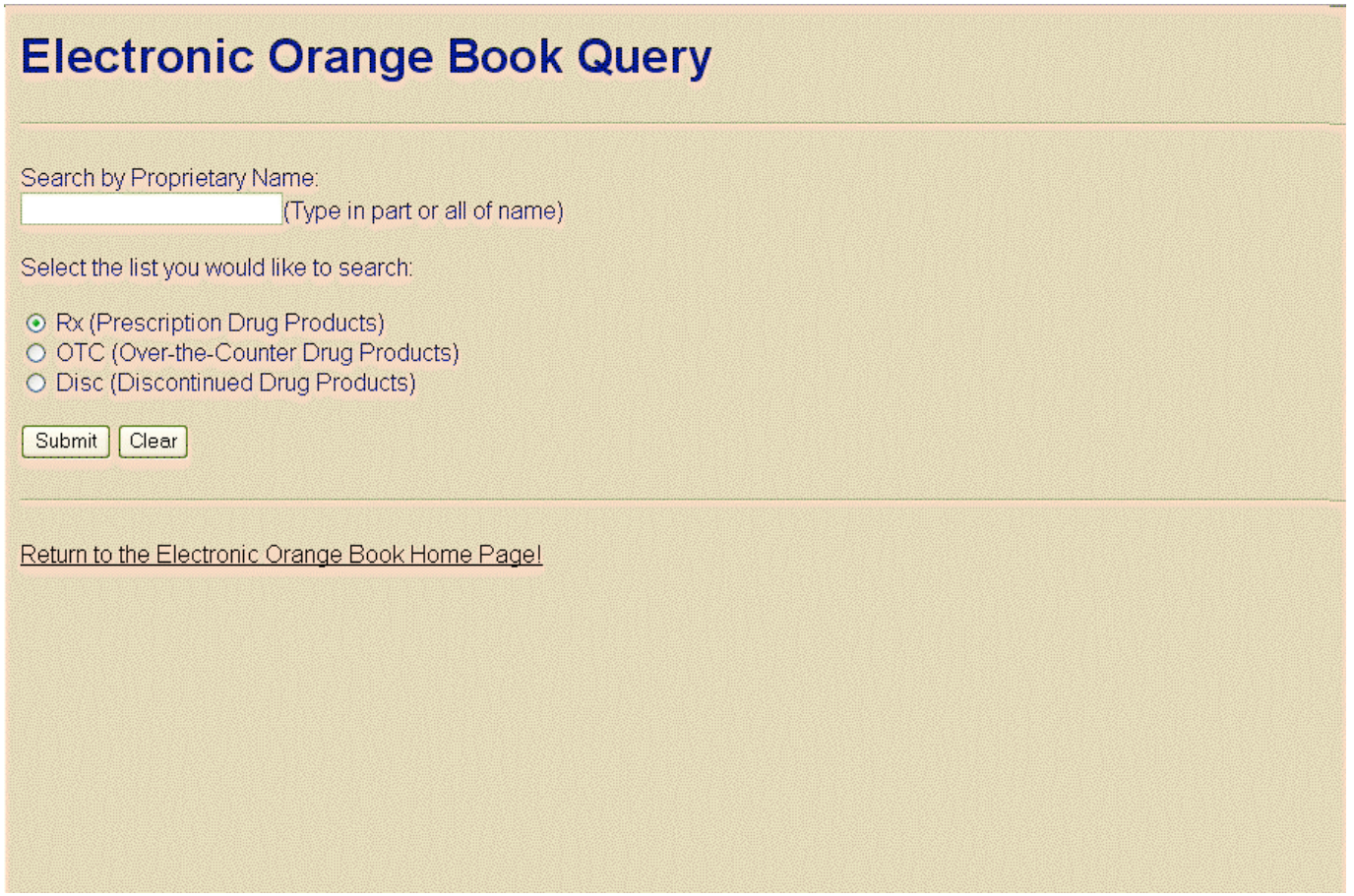
Search by Proprietary Name Search by Application Number

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!

Proprietary Name Search Results from "OB_Rx" table for query on "paxil."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
020710	AB	Yes	PAROXETINE HYDROCHLORIDE	SUSPENSION; ORAL	EQ 10MG BASE/5ML	PAXIL	GLAXOSMITHKLINE
020936	AB	No	PAROXETINE HYDROCHLORIDE	TABLET, EXTENDED RELEASE; ORAL	EQ 12.5MG BASE	PAXIL CR	GLAXOSMITHKLINE
020936	AB	No	PAROXETINE HYDROCHLORIDE	TABLET, EXTENDED RELEASE; ORAL	EQ 25MG BASE	PAXIL CR	GLAXOSMITHKLINE
020936		Yes	PAROXETINE HYDROCHLORIDE	TABLET, EXTENDED RELEASE; ORAL	EQ 37.5MG BASE	PAXIL CR	GLAXOSMITHKLINE
020031	AB	No	PAROXETINE HYDROCHLORIDE	TABLET; ORAL	EQ 10MG BASE	PAXIL	GLAXOSMITHKLINE
020031	AB	No	PAROXETINE HYDROCHLORIDE	TABLET; ORAL	EQ 20MG BASE	PAXIL	GLAXOSMITHKLINE
020031	AB	No	PAROXETINE HYDROCHLORIDE	TABLET; ORAL	EQ 30MG BASE	PAXIL	GLAXOSMITHKLINE
020031	AB	Yes	PAROXETINE HYDROCHLORIDE	TABLET; ORAL	EQ 40MG BASE	PAXIL	GLAXOSMITHKLINE

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

Search results from the "OB_Rx" table for query on "020710."

Active Ingredient:	PAROXETINE HYDROCHLORIDE
Dosage Form;Route:	SUSPENSION; ORAL
Proprietary Name:	PAXIL
Applicant:	GLAXOSMITHKLINE
Strength:	EQ 10MG BASE/5ML
Application Number:	020710
Product Number:	001
Approval Date:	Jun 25, 1997
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	**AB**
Patent and Exclusivity Info for this product:	View

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Patent and Exclusivity Search Results from query on Appl No 020710 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
020710	001	4721723	DEC 29,2006			
020710	001	4721723*PED	JUN 29,2007			
020710	001	5789449	JAN 06,2009			U-285
020710	001	5789449*PED	JUL 06,2009			U-285
020710	001	5811436	SEP 22,2015			
020710	001	5811436*PED	MAR 22,2016			
020710	001	5872132	MAY 19,2015			
020710	001	5872132*PED	NOV 19,2015			
020710	001	5900423	MAY 19,2015			
020710	001	5900423*PED	NOV 19,2015			
020710	001	6121291	MAR 17,2017			U-286
020710	001	6121291	MAR 17,2017			U-431
020710	001	6121291*PED	SEP 17,2017			U-431
020710	001	6121291*PED	SEP 17,2017			U-286
020710	001	6133289	MAY 19,2015			U-358
020710	001	6133289*PED	NOV 19,2015			U-358

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)(5).
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
3. Patents listed prior to August 18, 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
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 a 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

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Additional information:

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3. Patents listed prior to August 18, 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 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 added 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.
5. U.S. Patent Nos. RE 36481 and RE 36520 were relisted for Zocor (NDA 19-766) pursuant to the decision and related order in Ranbaxy Labs. v.Leavitt, No. 05-1838 (D.D.C. April 30, 2006). 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(j)(5)(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-0008 and 2005P-0046. Patents were subsequently delisted in the December 2006 Orange Book update as the exclusivity periods have triggered and run to expiration.

View a list of all patent use codes
View a list of all exclusivity codes

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Patent and Generic Drug Product Data Last Updated: August 17, 2007

Purpose of Paragraph IV Certifications and Notice Letters (continued)

- Types of Certification Letters

  21 U.S.C. § 355 (j)(2)(A)(vii)

  - 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

Purpose of Paragraph IV Certifications and Notice Letters (continued)

- Combining Different Paragraphs in Single Certification
  - Can Include Paragraph IV's and Paragraph III's in same Certification
  - 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)
    - NDA Holders listed in Orange Book
    - Patent Owners on Patent or recorded at USPTO
    - Multiple patents can mean multiple patent owners

United States Patent [19]

Barnes et al.

[11] **Patent Number: 4,721,723**

[45] **Date of Patent: Jan. 26, 1988**

[54] **ANTI-DEPRESSANT CRYSTALLINE PAROXETINE HYDROCHLORIDE HEMIHYDRATE**

[75] 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

[73] Assignee: **Beecham Group p.l.c.**, Brentford, England

[21] Appl. No.: **922,530**

[22] Filed: **Oct. 23, 1986**

[30] **Foreign Application Priority Data**

Oct. 25, 1985 [GB] United Kingdom 8526407
Oct. 25, 1985 [GB] United Kingdom 8526408

[51] **Int. Cl.**[4] **A61K 31/445; C07D 405/12**
[52] **U.S. Cl.** **514/321;** 546/197
[58] **Field of Search** 546/197; 514/321

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,007,196 2/1977 Christensen 546/197

OTHER PUBLICATIONS

Chemical Abstracts, 95:54664z (1981) [Goethert, M., et al., *Naunyn-Schmiedeberg's Arch. Pharmacol.* 1980, 313(1), 21–6].

J. B. Lassen, *Psychopharmacology,* 57, pp. 151–153 (1978).

J. B. Lassen, *European J. Pharmacol., 47, pp. 351–358 (1978).*

J. Lund et al., *Acta Pharmacol. et Toxicol.,* 44, pp. 289–295 (1979).

J. B. Lassen, et al., *Psychopharmacology,* 68, pp. 229–233 (1980).

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

[57] **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
    - Stay ends when lawsuit is resolved

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

Purpose of Paragraph IV Certifications and Notice Letters (continued)

- Benefit 180-Day Exclusivity Period (continued)
  - New Rule (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

- Minimum Statutory Requirements, 21 U.S.C §355 (j)(2)(B)(iv)
  - 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" 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 "willfulness"/"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 control; 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
      - *KSR v. Teleflex*, 127 S.Ct. 1727 (April 2007)
      - Reduces Showing Required by Generics
    - Enablement
    - Fraud on Patent Office
  - Difficult to prove, because of increased burden
  - 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
    - Narrows potential discovery
    - Risk exceptional case finding
  - 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

  21 U.S.C. 355 (j)(5)(C)(i)(III)

  - 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)

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
    - 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"

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)
    - Injunction against continued making, using , selling

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