CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-544

CHEMISTRY REVIEW(S)

NDA 21-544

Seasonale®

(levonorgestrel and ethinyl estradiol tablets)

0.15 mg / 0.03 mg

Reviewer: Suong Tran, PhD

Division of Reproductive and Urologic Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-544

2. REVIEW #: 1 of 1

3. REVIEW DATE: 28-AUG-2003

4. REVIEWER: Suong Tran, PhD

5. PREVIOUS DOCUMENTS: none

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document/DFS Date
Original	5-AUG-2002
Amendment	31-OCT-2002
Amendment	13-FEB-2003
Amendment	11-APR-2003
Amendment	14-APR-2003
Amendment	14-MAY-2003
Amendment	15-MAY-2003
Amendment	16-MAY-2003
Amendment	23-MAY-2003
Amendment	29-MAY-2003
Amendment	01-JUL-2003
Amendment	17-JUL-2003
Amendment	1-AUG-2003
Amendment	27-AUG-2003

7. NAME & ADDRESS OF APPLICANT:

Barr Research, Inc.
One Bala Plaza, Suite 324
Bala Cynwyd, PA 19004

8. DRUG PRODUCT NAME/CODE/TYPE:

Drug product name:
Seasonale® (levonorgestrel/ethinyl estradiol tablets) 0.15 mg/0.03 mg
Proprietary Name: Seasonale®
Non-Proprietary Name (USAN): levonorgestrel and ethinyl estradiol
Code Name/# (OGD only): Not Applicable
Chem. Type(ONDC only): 3
Submission Priority(ONDC only): S

9. LEGAL BASIS FOR SUBMISSION: Not Applicable

10. PHARMACOL. CATEGORY: oral contraceptive

11. DOSAGE FORM: immediate-release tablet

12. STRENGTH/POTENCY: 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol

13. ROUTE OF ADMINISTRATION: oral administration

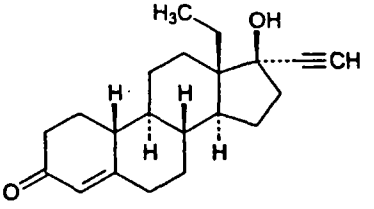
14. Rx/OTC DISPENSED: _x_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

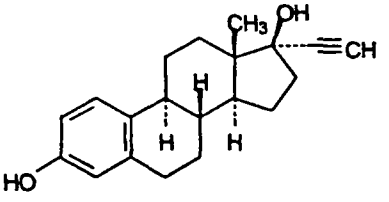
____SPOTS product – Form Completed

_x_Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Levonorgestrel, USP (USAN name):
18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, (17α)-, (-)-
CAS-797-63-7
Molecular formula: $C_{21}H_{28}O_2$
Molecular weight: 312.45



Ethinyl Estradiol USP (USAN name)
19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-
CAS-57-36-6
Molecular formula: $C_{20}H_{24}O_2$
Molecular weight: 296.41

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	[redacted]	3	Adequate	30-MAR-2001	By Chemist N. Takiar
[redacted]	II	[redacted]	[redacted]	3	Adequate	23-MAY-2003	By Chemist N. Takiar
[redacted]	II	[redacted]	[redacted]	3	Adequate	01-MAY-2002	By Chemist A. Raw
[redacted]	III	[redacted]	[redacted]	3	Adequate	14-JUN-2002	By Chemist L. Rocca
[redacted]	III	[redacted]	[redacted]	3	Adequate	19-AUG-2000	By Chemist R. Frankewich

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
ANDA	75-866	Portia™ (levonorgestrel 0.15 mg and ethinyl estradiol 0.03 mg tablets, USP)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	*Not Applicable*		
EES	**Acceptable**	2-JUN-2003	J. D'Ambrogio
Pharm/Tox	*Not Applicable*		
Biopharm	**Acceptable**	21-MAY-2003	M.-J. Kim

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
	(Dissolution acceptance criteria Q = — 45 minutes for both drug substances)		
LNC	*Not Applicable*		
Methods Validation	Package will be submitted to FDA labs.		
DMETS	**Acceptable name "Seasonale"**	15-AUG-2003	S. Dallas
EA	*Not Applicable*		
Microbiology	*Not Applicable*		

19. ORDER OF REVIEW (OGD Only) Not Applicable

APPEARS THIS WAY
ON ORIGINAL

The Executive Summary

Recommendations

A. Recommendation and Conclusion on Approvability

The final recommendation from Chemistry is APPROVAL.
Refer to the Basis for Approval in Section C below for details.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product subject of this NDA 21-544 is the same as the marketed Portia, which was approved by the Office of Generic Drug on 23-MAY-2002 under ANDA 75-866. The approved ANDA product is packaged for a 28-day regimen, while the NDA product is packaged for a 91-day regimen. The applicant and manufacturers are the same for both products. The ANDA is cross-referenced for all CMC information. However, additional information as well as several changes to the information were requested by this chemist for the NDA 21-544. Refer to the discussion below for details.

Drug product –

- Name: Seasonale® (levonorgestrel and ethinyl estradiol tablets) 0.15 mg/0.03 mg
- Strength: 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol
- Dosage form: immediate release tablet for oral administration
- Indication: oral contraceptive
- Formulation: Inactive ingredients are Anhydrous Lactose NF, Magnesium Stearate NF, hydroxylpropylmethyl cellulose USP, Microcrystalline Cellulose NF, and [redacted]. All inactive ingredients except the color coat [redacted] are compendial excipients; the color coat is the same as approved in ANDA 75-866 for Portia.
- Packaging: (from the outside in) one carton contains a full physician insert and three aluminum pouches; each pouch contains a patient insert, a desiccant packet, and a plastic tablet dispenser/compact; one tablet dispenser/compact opens (like a book) to have three plastic leaves, each leaf containing one blister card; the top two blister cards each contains 28 pink active tablets, and the third blister card on the bottom contains 28 pink active tablets followed by 7 white placebo tablets.. The blister cards are composed of a lidding foil (product-contact surface: [redacted] and a film [redacted]. The product-contact surface components are the same as those in the packaging system approved in ANDA 75-866 for Portia.
- The only difference between the clinical batches and the drug product intended for marketing is the color of the film coats, [redacted] and pink, respectively. A bridging

bioequivalence study was conducted comparing the [redacted] and pink tablets (refer to the Clin. Pharm. reviews).

- The only difference between the NDA product and the approved ANDA product is the code debossed on the tablet. For the NDA, the active Seasonale tablet is debossed with "S" on the top and "62" on the bottom, and the placebo is debossed with "S" on the top and [redacted]197" on the bottom. For the approved ANDA, the active Portia tablet is debossed with "B" on the top and "992" on the bottom, and the placebo is debossed with "B" on the top and "208" on the bottom. The Clin. Pharm. reviewer (M.-J. Kim) indicated that no dissolution study is required to compare the two debossed active tablets (private communication).
- The dissolution acceptance criteria for Portia of ANDA 75-866 are Q = [redacted], 60 minutes. The same criteria were proposed by the applicant for Seasonale. However, based on the dissolution profiles of the clinical batches as well as stability data, this reviewer and the Clin. Pharm. reviewer (M.-J. Kim) determined that the criteria should be Q = [redacted] 45 minutes for both drug substances. The applicant agreed to FDA's proposal and submitted the final drug product specification in the 23-MAY-2003 amendment.
- Per FDA's agreement at the pre-NDA meeting on 23-APR-2002, stability data are provided for [redacted] batches of the ANDA product to support the expiry of the NDA product. The approved Portia is packaged for a 28-day regimen (one blister card with 28 tablets), while the NDA product Seasonale is packaged for a 91-day regimen (two blisters cards each with 28 tablets and one blister card with 35 tablets). The product-contact components of the primary packaging are the same for both products. However, the dimensions of the blister cards are different for Portia and Seasonale, with the space between cavities and card edges being the most critical difference. Since stability data for Portia are being used to support an expiry for Seasonale, this reviewer requested additional data in order to show the equivalence of sealing integrity between the blister card of Portia and the blister cards of Seasonale. The applicant submitted the data per USP 25 <671> Containers-Permeation (specifically for blisters) in the 13-FEB-2003 and 14-APR-2003 amendments. The data show that the sealing integrity is equivalent when comparing the Portia 28-tablet blister to the Seasonale 35-tablet or 28-tablet blister. In addition, the Seasonale container/closure system has the blisters packaged inside a compact, which is wrapped in an aluminum pouch with a desiccant packet, which should provide ample protection against moisture permeation.
- Expiry is 18 months at room temperature. This expiry is based on satisfactory [redacted] long-term data for [redacted]ortia [redacted] batches in blisters, [redacted] long-term and accelerated data for [redacted]ortia [redacted] batch in blisters with pouch and desiccant, and [redacted]ong-term and accelerated data for [redacted]easonale [redacted] batch in blisters with pouch and desiccant. Note: The last batch has limited stability data because the levonorgestrel from [redacted] was obtained only after 11-MAR-2003 (the date when the original drug substance manufacturer [redacted] abruptly discontinued the supply of levonorgestrel to the applicant).
- The established names "(0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol)" currently in the labeling of the generic Portia were found to be unacceptable by this reviewer and DMETS. The applicant agreed to change them to "(levonorgestrel/ethinyl estradiol tablets) 0.15mg/0.03 mg" for Seasonale (15-MAY-2003 amendment). In addition, per this reviewer's request, [redacted] are printed on the blister card.

- Reference is made to Drug Master Files [redacted] and [redacted] and [redacted] for all chemistry reviews of these drug substances. DMF [redacted] was found to be adequate by Chemist N. Takiar on 30-MAR-2001, and DMF [redacted] was found to be adequate by Chemist N. Takiar on 23-MAY-2003. DMF [redacted] was found to be adequate by Chemist A. Raw on 01-MAY-2002.
- The chemical names for levonorgestrel and ethinyl estradiol currently in the labeling of the generic Portia were found to be non-compendial by this reviewer. The applicant agreed to change the names, and the compendial chemical names are now used in the labeling of Seasonale (27-AUG-2003 amendment).

B. Description of How the Drug Product is Intended to be Used

- Dosage administration: oral
- Dosing schedule: one tablet per day
- Dosage strength: 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol per tablet
- Expiry: 18 months at room temperature.

C. Basis for Approvability or Not-Approval Recommendation

- The initial review by this chemist found several deficiencies in the NDA. Subsequently, per FDA's requests for additional information, the applicant submitted amendments (dated 31-OCT-2002, 13-FEB-2003, 11-APR-2003, 14-APR-2003, 14-MAY-2003, 15-MAY-2003, 16-MAY-2003, 23-MAY-2003, 1-JUL-2003, 17-JUL-2003, 1-AUG-2003, and 27-AUG-2003) which satisfactorily resolved the chemistry deficiencies.
- Final package insert and mock-up container labels were submitted in the 27-AUG-2003 amendment and are satisfactory.
- The Office of Compliance issued an "Acceptable" recommendation on 2-JUN-2003 in the establishment evaluation report.
- The Division of Medical Errors and Technical Support (DMETS) found the proprietary name "Seasonale" acceptable on 15-AUG-2003 (S. Dallas).

Administrative

A. Reviewer's Signature

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B. Endorsement Block

Electronically captured in DFS

C. CC Block

Electronically captured in DFS

16 Page(s) Withheld

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Suong Tran
8/28/03 12:46:04 PM
CHEMIST

revised and final paper copy 8/28/03

Moo-Jhong Rhee
8/28/03 01:28:56 PM
CHEMIST
I concur