CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74-845

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS

DIVISION OF CHEMISTRY II

ANDA REVIEW

1. CHEMIST'S REVIEW NO. 6

2. ANDA # 74-845

3. NAME AND ADDRESS OF APPLICANT

Biovail Corporation International
460 Comstock Road
Toronto, Ontario, Canada M1L 4S4

4. LEGAL BASIS for ANDA SUBMISSION

Reference Drug: Cardizem SR Capsules, Marion Merrell Dow; patent expiration for patent #4721619 - 1.26.2005

5. SUPPLEMENT(s) None

6. PROPRIETARY NAME

None

7. NONPROPRIETARY NAME

Diltiazem Hydrochloride Extended-release Capsules

SUPPLEMENT(s) PROVIDE(s) FOR: None

9. AMENDMENTS AND OTHER DATES:

Firm:

01.31.96 - Original submission
03.28.96 - Amendment
05.08.96 - Amendment
02.11.97 - Amendment
08.28.97 - Amendment
3-26-98 - Amendment for Bic
7-13-98 - Amendment
7-28-98 - Amendment
9-24-98 - Amendment - Pat. Certification
8-24-99 - Amendment

FDA:

03.18.96 - Refuse to file
04.15.96 - Refuse to file
05.20.96 - Acceptable to file
11.27.96 - NA letter #1
08.04.97 - NA facsimile
6-30-98 - NA letter # 3

9-24-98 - Telephone Request# 4
1-9-99 - NA minor letter # 5

10. PHARMACOLOGICAL CATEGORY

Anti-hypertensive

11. Rx or OTC

Rx

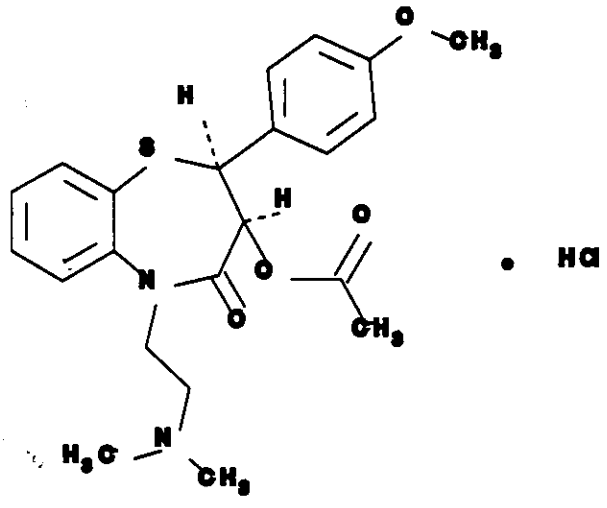
12. RELATED IND/NDA/DMF(s) See review element# 37

13. DOSAGE FORM
Extended-release

14. POTENCY
60, 90, 120 mg Capsules

15. CHEMICAL NAME AND STRUCTURE

Diltiazem Hydrochloride USP
$C_{22}H_{26}N_2O_4S.HCl$; M.W. = 450.98



(+)-5-[2-(Dimethylamino)ethyl]-*cis*-2,3-dihydro-3-hydroxy-2-(*p*-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one acetate (ester) monohydrochloride. CAS [33286-22-5]

16. RECORDS AND REPORTS None

17. COMMENTS

Telephone amendment:

Q: Please submit the revised finished product test specification form.

A: The revised finished product test specification form was submitted on September 24, 1998 and found acceptable by Florence Fang (see OGD Approval Routing Summary).

Status:

a. EER status: Acceptable

EER was acceptable on 1-15-97. The updated EER was requested on 5-7-98 by T Ames and found acceptable on August 30, 1999.

b. Method Validation status: N/A, however, Pending for dissolution testing method.

Compendial articles, test, methods and specifications are compendial except for dissolution test for drug product. MV package for the drug release specifications and method has been sent to New York District Laboratory on July 22, 1998. Firm made a commitment to assisting the district Lab. during its evaluation of the test method and specifications, to provide support as required and to resolve any issues which may arise.

c. Bio-review status: Satisfactory

Satisfactory per L. Chuang reviewed on 3-26-98.

d. Labeling review status: **Satisfactory**

Satisfactory per A. Vezza on 1-2-98.

e. DMF Satisfactory

The DMF was found acceptable by L. Tang on 7-24-98.

18. CONCLUSIONS AND RECOMMENDATIONS

Approvable, however, MV package for the drug release specifications and method has been sent to New York District Laboratory on July 22, 1998. Bioval made the following commitments:

1. Interim approved dissolution specifications will be used to test process validation batches. This data will be forwarded to the Division of Chemistry II as soon as it becomes available.

2. To provide support to the FDA district laboratory during its evaluation of the test method and specifications.

19. REVIEWER: DATE COMPLETED:

Lucia C. Tang 9-3-99

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Commercial/Confidential

Information and are not

releasable.

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releasable.

6/30/98

Chemistry comments

#3P