CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-093

CHEMISTRY REVIEW(S)

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-093 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 6-27-2000

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	28-Sep-99	28-Sep-99	28-Sep-99
Amendment	22-Dec-99	12-Dec-00	01-Jan-00
	27-Jan-00	28-Jan-00	9-Feb-00
	30-Mar-00	31-Mar-00	31-Apr-00
	31-Mar-00	3-Apr-00	10-Apr-00
	19-May-00	22-May-00	23-May-00
	16-Jun-00	19-Jun-00	19-Jun-00

AMENDMENTS PROVIDES FOR:

1. 12 Months stability update. Modification of 75 mL HDPE bottle and analytical characterization of a new batch of candesartan cilexetil analytical reference standard.
2. General correspondence concerning the synthesis of Candesartan cilexetil.
3. 18 Months stability update and statistical analysis.
4. Manufacturing batch record data previously submitted for ATACAND™ Tablets.
5. Updated information regarding clinical supplies used in bio-studies, comparison dissolution profile studies requested by Biopharm and corresponding batch numbers for formulations given in Tables 4.119 thru 4.121.
6. Response to telephone questions regarding this submission, made May 19, 2000.

NAME & ADDRESS OF APPLICANT:

AstraZeneca L.P.
Address: 725 Chesterbrook Blvd.
Wayne, PA 19087-5677
Responsible Official: Cindy M. Lancaster
Dir. - Reg. Affairs
Phone: (610) 695-1370
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E-mail: www.astrazeneca-us.com

Proprietary:	**ATACAND HCT™ Tablets**
Nonproprietary:	Candesartan cilexetil-hydrochlorothiazide tablets
CAS Registry Number:	145040-37-5 (CC)/58-93-5 (HCTZ)
Code Names:	[CC]TCV-116(Takeda)and H 212/91(AstraMerck)/HCT
Chemical type/Therapeutic Class:	4S
Special Products:	__Yes _X_No

Patent Status: (B1.1, 013-001-031 and 2)

Patent Number	Patent Expiration Date	Type of Patent	Patent Owner	Authorized Representative to Receive Notice of Patent Certification
*5,196,444	April 18, 2011	drug substance; drug product; method of use	Takeda Chemical Industries, Ltd.	AstraZeneca LP
*5,534,534	July 9, 2013	drug product	Takeda Chemical Industries, Ltd.	AstraZeneca LP
*5,703,110	April 18, 2011	drug substance; drug product; method of use	Takeda Chemical Industries, Ltd.	AstraZeneca LP
*5,705,517	April 18, 2011	drug substance; drug product; method of use	Takeda Chemical Industries, Ltd.	AstraZeneca LP
5,721,263	February 24, 2015	drug product; method of use	Takeda Chemical Industries, Ltd.	AstraZeneca LP

*Patent previously identified under NDA 20-838 (candesartan cilexetil).

PHARMACOL.CATEGORY/INDICATION:

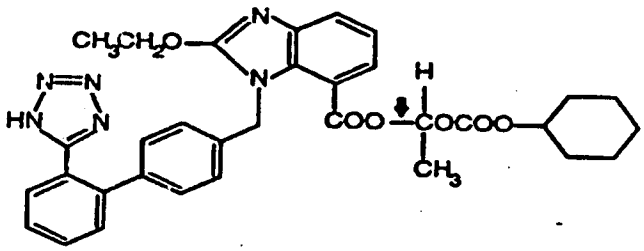
As per 356h, none.

Treatment of hypertension, non-peptide, AT_1-subtype Angiotensin II Receptor Antagonist.

DOSAGE FORM: Tablet
STRENGTHS: 16-12.5 mg. and 32-12.5 mg. CC-HCTZ/tablet
ROUTE OF ADMINISTRATION: Oral
DISPENSED: X Rx ____ OTC

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

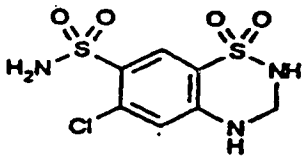
Candesartan cilexetil:



⬇ site of ester hydrolysis.

Molecular Formula: $C_{33}H_{34}N_6O_6$
Molecular Weight: 610.67 daltons
Chemical Name: (±)-1-(cyclohexyloxycarbonyloxy)ethyl-2-ethoxy-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylate

Hydrochlorothiazide:



Molecular Formula: $C_7H_8ClN_3O_4S_2$

Molecular Weight: 297.75 daltons

Chemical Name: 6-Chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide

SUPPORTING DOCUMENTS:

NDA 20-838 Candesartan cilexetil tablets for congestive heart failure

RELATED DOCUMENTS (if applicable):

DMF	Holder	Type	Operation	Status/LOA
		II		OK-L. Tang/ 7-14-99 B1.1, 11
		III		OK J. Piechocki/ 8-11-99 B1.1, 27
		III		OK - E. Duffy 4/9/92 B1.1, 29
		III		OK - Danae D. Christodoulou B1.1, 16
		III		OK - Nashed E. Nashed 7/2/96 B1.1, 17
		III		OK - James D. Videre 9/1/99 B1.1, 18
		III		OK - Joe Sieczkowski 6/17/99 B1.1, 21
		III		OK - Florian Zielinski 1/6/95/ B1.1, 14
		III		OK - Dale L. Koble 3/2/97 B1.1, 25
		III		OK - R.H. Sievers 10/27/97 B1.1, 23
		II		OK - Maria Elena Ysern 11/1/99 B1.1, 19
?		II		Not Applicable
		II		OK - Approved as part of NDA 20-838

CONSULTS:

OPDRA was consulted on the Tradename Status for this product and has no objection to the proposed name ATACAND HCT. (J. Phillips - 3/3/2000, copy attached.

REMARKS/COMMENTS:

This is a new combination product consisting of a previously approved and marketed product ATACAND HCT™ Tablets with HCTZ.

The firm has submitted a request for Categorical Exclusion from the Environmental Impact Statement and it is acceptable.

The firm has been deemed acceptable, by profile, by the Inspection Branch.

Biopharm recommends they change the Q to • min for the 32-12.5 dosage strength.

CONCLUSIONS & RECOMMENDATIONS:

The firm should be apprised of the following deficiencies:

1. They have not submitted the requisite data to qualify their new reference standard as such.
2. The firm has not submitted data to demonstrate that their formulation and dosage form is stable to UV-A radiation as per the ICH recommended guideline or an alternative procedure.
3. The firm needs to change their dissolution specification for the 32-12.5 dosage strength to in

/S/

6/27/2000

Joseph T. Piechocki, Ph.D.
Review Chemist

cc:

Orig. NDA 21-093
HFD-110/Division File
HFD-110/~~PiechockiJ/6/27/2000~~ FZIELINSKI/PM/KSRINIVASACHAR
HFD-810/JSIMMONS
~~District~~
~~HFD-102/~~

/S/
6-30-00