CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-078

CHEMISTRY REVIEW(S)

HFD-590 / Jansen

DIVISION OF SPECIAL PATHOGEN AND IMMUNOLOGIC DRUG PRODUCTS — HFD-590

JUN 23 2000

Review of Chemistry, Manufacturing and Controls Section

NDA #: 21-078

CHEMISTRY REVIEW #: 2 **REVIEW COMPLETED:** June 20, 2000

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
BC	07/29/99	07/30/99	--
BC	12/21/99	12/22/99	--
NC	01/10/00	01/11/00	--
BC	01/12/00	01/13/00	--
AC (?)	01/19/00	01/21/00	--
BC	01/19/00	01/21/00	--
BC	02/11/00	02/14/00	--
BC	03/21/00	03/22/00	--
BC	04/19/00	04/20/00	--

NAME/ADDRESS OF SPONSOR: Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

DRUG PRODUCT NAME:
Proprietary: MALARONE™
Nonproprietary: Atovaquone and Proguanil Hydrochloride Tablets

CHEM. TYPE/THER. CLASS: 4P

DRUG CLASS: --

PHARMACOLOGICAL CATEGORY: antimalarial

INDICATION: Treatment and Prevention of Malaria

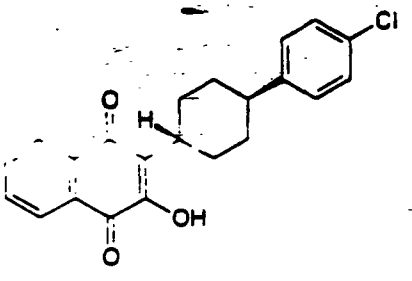
DOSAGE FORM/STRENGTH: Tablets
250 mg Atovaquone/100 mg Proguanil HCl
62.5 mg Atovaquone/25 mg Proguanil HCl

ROUTE OF ADMINISTRATION: Oral

CHEMICAL NAME/STRUCTURAL FORMULA:

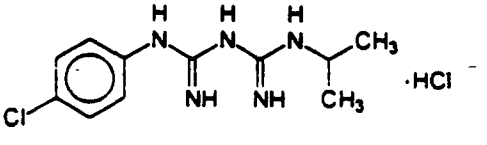
Atovaquone

trans-2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone



Proguanil HCl

1-(4-Chlorophenyl)-5-isopropyl biguanide hydrochloride



	Atovaquone	Proguanil HCl
CAS Registry:	95233-18-4	637-32-1
Molecular Formula:	$C_{22}H_{19}ClO_3$	$C_{11}H_{17}Cl_2N_5$ ($C_{11}H_{16}ClN_5 \cdot HCl$)
Molecular Weight:	366.84	290.21

SUPPORTING DOCUMENTS:

DMF ——; (type II: ——). Deemed inadequate on 03/22/99. Adequate as of amendment dated 05/2?/99. Re-reviewed after amendments of 06/16/99. 02/10/00, 03/06/00, and 05/26/00: adequate.

DMF —— (type IV)

DMF —— (type III)

DMF —— (type III)

DMF ——

DMF ——

DMF ——

RELATED DOCUMENTS:

NDA 20-259	MEPRON (atovaquone) Tablets
NDA 20-500	MEPRON (atovaquone) Suspension
IND ——	
IND ——	MALARONE

REMARKS/COMMENTS:

DRUG SUBSTANCE — The data on atovaquone was found to be adequate in the first review, mostly on the basis of prior approvals of Mepron® Tablets. The data on proguanil HCl was mostly contained in DMF —. The initial inspection of the DMF holder resulted in a Withhold recommendation from OC. The site was re-inspected on two more occasions before the field considered the firm ready for approval.

DRUG PRODUCT — During the first review, the atovaquone dissolution test was withdrawn upon request and the acceptance criteria for some impurities were reduced upon request. The originally proposed blister packaging, which was not child resistant, was replaced with — bottles with —closures. The firm requested a 30-month expiry for the bottles. Method validation was completed and the methods were found to be satisfactory (with minor comments).

LABELING — The labeling was revised after the first review to indicate a different market package.

ENVIRONMENTAL ASSESSMENT — Categorical exclusion (see review #1).

CONCLUSIONS & RECOMMENDATIONS:

Recommend APPROVAL.

John Smith, Review Chemist

Concurrence: 6/26/00

HFD-590/NSchmuff

cc:

Orig. IND	HFD-590/VJensen
HFD-590/Div. File	HFD-590/SKunder
HFD-590/NSchmuff	HFD-590/SBala
HFD-590/AMeyerhoff	HFD-590/JSmith

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DIVISION OF SPECIAL PATHOGEN AND IMMUNOLOGIC DRUG PRODUCTS — HFD-590

Review of Chemistry, Manufacturing and Controls Section

NDA #: 21-078

CHEMISTRY REVIEW #: 1 **REVIEW COMPLETED:** June 29, 1999

ADDENDUM

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
N000	12/29/98	12/30/98	01/05/99

NAME/ADDRESS OF SPONSOR: Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

DRUG PRODUCT NAME:

Proprietary: MALARONE™

Nonproprietary: Atovaquone and Proguanil Hydrochloride Tablets

CHEM. TYPE/THER. CLASS: 4P

DRUG CLASS: --

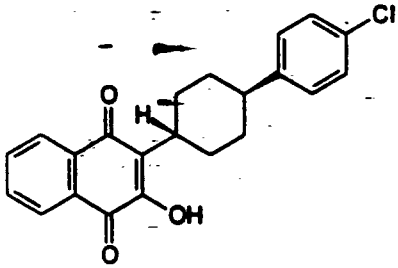
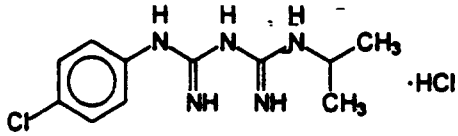
PHARMACOLOGICAL CATEGORY: antimalarial

INDICATION: Treatment and Prevention of Malaria

DOSAGE FORM/STRENGTH: Tablets
250 mg Atovaquone/100 mg Proguanil HCl
62.5 mg Atovaquone/25 mg Proguanil HCl

ROUTE OF ADMINISTRATION: Oral

CHEMICAL NAME/STRUCTURAL FORMULA:

Atovaquone	Proguanil HCl
(±) *trans*-2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone	1-(4-Chlorophenyl)-5-isopropyl biguanide hydrochloride
	
CAS Registry: 95233-18-4	637-32-1
Molecular Formula: $C_{22}H_{19}ClO_3$	$C_{11}H_{17}Cl_2N_5$ ($C_{11}H_{16}ClN_5 \cdot HCl$)
Molecular Weight: 366.84	290.21

SUPPORTING DOCUMENTS:

DMF [redacted] (type II; [redacted]. Deemed inadequate on 03/22/99. Adequate as of amendment dated 05/28/99.

DMF [redacted] (type IV)

DMF [redacted] (type III)

DMF [redacted] (type III)

RELATED DOCUMENTS:

NDA 20-259	MEPRON (atovaquone) Tablets
NDA 20-500	MEPRON (atovaquone) Suspension
IND [redacted]	
IND [redacted]	MALARONE

REMARKS/COMMENTS:

DRUG SUBSTANCE — The data on atovaquone was found to be approvable mostly on the basis of prior approvals of Mepron® Tablets. The data on proguanil HCl was mostly contained in DMF [redacted], which was found to be Inadequate in the initial review. The amended DMF was considered adequate. The initial inspection of the DMF holder resulted in a Withhold recommendation from OC. **The site was re-inspected in June, 1999 and OC again issued a Withhold recommendation.**

DRUG PRODUCT — The atovaquone dissolution test was withdrawn upon request. Acceptance criteria for some impurities were reduced upon request. The proposed blister packaging is not child resistant, though it is arguable whether it needs to be. **Method validation was not completed as of 06/15/99 (not required for approval).**

LABELING — The proposed trade name, Malarone, was found to be unsatisfactory by the CDER Labeling and Nomenclature Committee; however, this recommendation was overruled by the reviewing division. Otherwise, only minor chemistry issues.

ENVIRONMENTAL ASSESSMENT — Categorical exclusion.

CONCLUSIONS & RECOMMENDATIONS:

— **The original review was completed in anticipation (based on the information available at the time) that the [redacted] site would be found satisfactory by the inspection that was in progress in June, 1999. However, as a result of continuing problems with the site, the Office of Compliance again recommended that approval be withheld until cGMP deficiencies are corrected.**

Recommend APPROVABLE.

JS 6/29/99

John Smith, Review Chemist

Concurrence:
HFD-590/NSchmuff JS 6/29/99

cc:

Orig. IND	HFD-590/CSO
HFD-590/Div. File	HFD-590/P/T
HFD-590/ NSchmuff	HFD-590/Micro
HFD-590/MO	HFD-590/JSmith

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DIVISION OF SPECIAL PATHOGEN AND IMMUNOLOGIC DRUG PRODUCTS — HFD-590

Review of Chemistry, Manufacturing and Controls Section

NDA #: 21-078

CHEMISTRY REVIEW #: 1 **REVIEW COMPLETED:** June 16, 1999

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
N000	12/29/98	12/30/98	01/05/99
BC	04/21/99	04/22/99	--
BC	04/21/99	04/22/99	--
BC	05/17/99	05/18/99	--
BC	06/03/99	--	--
BC	06/04/99	--	--
BC	06/10/99	--	--
BC	06/14/99	--	--
BC	06/15/99	--	--

NAME/ADDRESS OF SPONSOR: Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

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Proprietary: MALARONE™

Nonproprietary: Atovaquone and Proguanil Hydrochloride Tablets

CHEM. TYPE/THER. CLASS: 4P

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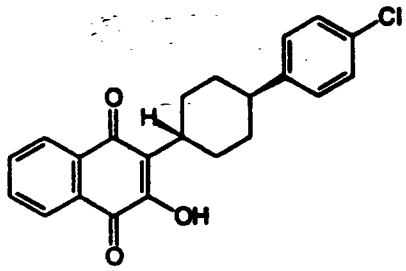	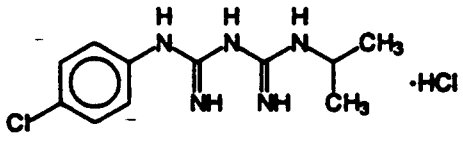
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DMF — — (type IV)

DMF — (type III)

DMF — — (type III)

RELATED DOCUMENTS:

NDA 20-259	MEPRON (atovaquone) Tablets
NDA 20-500	MEPRON (atovaquone) Suspension
IND —	
IND —	MALARONE

REMARKS/COMMENTS:

DRUG SUBSTANCE — The data on atovaquone was found to be approvable mostly on the basis of prior approvals of Mepron® Tablets. The data on proguanil HCl was mostly contained in DMF — which was found to be Inadequate in the initial review. The amended DMF was considered adequate. **The initial inspection of the DMF holder resulted in a Withhold recommendation from OC. The site has been re-inspected.**

DRUG PRODUCT — The atovaquone dissolution test was withdrawn upon request. Acceptance criteria for some impurities were reduced upon request. The proposed blister packaging is not child resistant, though it is arguable whether it needs to be. **Method validation was not completed as of 06/15/99 (not required for approval).**

LABELING — The proposed trade name, Malarone, was found to be unsatisfactory by the CDER Labeling and Nomenclature Committee; however, this recommendation will evidently be overruled by the reviewing division. Otherwise, only minor chemistry issues (trade names were used for some inactive ingredients, only cartons (not blister packaging) were mentioned in the How Supplied section, the proposed storage temperature statement was not in accord with "current Agency thinking").

ENVIRONMENTAL ASSESSMENT — Categorical exclusion.

CONCLUSIONS & RECOMMENDATIONS:

Final recommendation from the Office of Compliance is still pending. However, based on informal communications with the field, it is expected that OC will recommend approval. Therefore:

Recommend APPROVAL.

JS 6/16/99
John Smith, Review Chemist

Concurrence:
HFD-590/NSchmuff JS 6/16/99

cc:

Orig. IND	HFD-590/CSO
HFD-590/Div. File	HFD-590/P/T
HFD-590/ NSchmuff	HFD-590/Micro
HFD-590/MO	HFD-590/JSmith

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WITHHOLD 7 PAGE (S)

Application: NDA 21078/000
Stamp: 30-DEC-1998
Regulatory Due: 21-JUL-2000
Applicant: GLAXO WELLCOME
5 MOORE DR
RESEARCH TRIANGLE PARK, NC 27709
Priority:
Org Code: 4P

Action Goal:
District Goal: 24-NOV-1999
Brand Name: MALARONE (ATOVAQUONE/PROGUANIL HCL) TABL
Estab. Name:
Generic Name: ATOVAQUONE/PROGUANIL HCL

Dosage Form: (TABLET)
Strength: 250/100 MG, 62.5/25 MG

FDA Contacts: M. DEMPSEY (HFD-440) 301-827-3176 , Project Manager
J. SMITH (HFD-590) 301-827-2175 , Review Chemist
N. SCHMUFF (HFD-590) 301-827-2425 , Team Leader

Overall Recommendation: WITHHOLD on 28-JUN-1999 by B. HARTMAN (HFD-324) 301-827-0067
ACCEPTABLE on 19-MAY-2000 by P. ALCOCK (HFD-324) 301-827-0062
WITHHOLD on 11-MAR-1999 by R. WOODS (HFD-324) 301-827-0062
WITHHOLD on 03-NOV-1999 by M. EGAS (HFD-322) 301-594-0095

Establishment: 9610411
GLAXO OPERATIONS UK LTD
WARE, HERTFORDSHIRE, UK
DMF No:
AADA:
Responsibilities: FINISHED DOSAGE OTHER TESTER
Profile: CTL
OAI Status: NONE
Estab. Comment: ACTUALLY PARK RD ADDRESS. NO NEED TO INSPECT IF ONLY INVOLVED IN NDA BATCHES. PARK RD HAS NO CFN. (on 05-FEB-1999 by M. EGAS (HFD-322) 301-594-0095)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	12-JAN-1999				SMITHJ
OC RECOMMENDATION	12-JAN-1999			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment: 9615283
GLAXO WELLCOME INC
L5N 6L 4
MISSISSAUGA, ONTARIO, CA
DMF No:
AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER
Profile: TCM
OAI Status: NONE
Estab. Comment: SOME STABILITY TESTING OF NDA BATCHES; NO ROLE IN PRODUCTION (on 12-JAN-1999 by J. SMITH (HFD-590) 301-827-2175)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	12-JAN-1999				SMITHJ
SUBMITTED TO DO	12-JAN-1999	PS			FERGUSONS
DO RECOMMENDATION	27-JAN-1999			ACCEPTABLE BASED ON FILE REVIEW	DAMBROGIOJ
EI 6/15-18/98 OC RECOMMENDATION	27-JAN-1999			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

Establishment: 9610414
GLAXO WELLCOME OPERATIONS UK

24-NOV-1999

21-JUL-2000
GLAXO WELLCOME
590
Priority:
Org Code:
Application Comment:

DA1 5AH
DARTFORD, KENT, UK
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE OTHER TESTER
Profile: CSN OAI Status: NONE
Estab. Comment: ALSO MFG NDS ATOVAQUONE (on 05-FEB-1999 by M. EGAS (HFD-322) 301-594-0095)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	05-FEB-1999				EGASM
OC RECOMMENDATION	05-FEB-1999			ACCEPTABLE BASED ON PROFILE	EGASM

Profile: CTL OAI Status: NONE
Estab. Comment: SOME MANUFACTURING OF, AND RELEASE & STABILITY TESTING OF, NDA BATCHES; NO ROLE IN PRODUCTION (on 12-JAN-1999 by J. SMITH (HFD-590) 301-827-2175)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	12-JAN-1999				SMITHJ
SUBMITTED TO DO	12-JAN-1999	GMP			FERGUSONS
DO RECOMMENDATION	27-JAN-1999			ACCEPTABLE BASED ON FILE REVIEW	DAMBROGIOJ
EI 4/21-24/97					
OC RECOMMENDATION	27-JAN-1999			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

Establishment: [redacted]
DMF No: [redacted] AADA:
Responsibilities: [redacted]
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	12-JAN-1999				SMITHJ
SUBMITTED TO DO	12-JAN-1999	10D			FERGUSONS
ASSIGNED INSPECTION	12-JAN-1999	PS			RBROWN4
INSPECTION PERFORMED	16-FEB-1999		12-FEB-1999		RBROWN4
DO RECOMMENDATION	16-FEB-1999			WITHHOLD BPC PROCESS VALIDATION INADEQUATE LAB CONTROLS INSUFFICIENT DEVELOPMENT	RBROWN4

DATA

NEW JERSEY DISTRICT PAI SHOWED UNINVESTIGATED UNREPORTED ASSAY FAILURES AND AN IMPURITY AT [redacted] PURIFICATION PROCESS NOT VALIDATED, TEST METHOD [redacted] VALIDATION DATA FOR ACCURACY AND LINEARITY MISSING, LACK OF TM STABILITY INDICATION EVIDENCE AND NO APPROVAL OF TM AS VALIDATED AND "SUITABLE" FOR USE.

EIR RECEIVED BY OC	01-MAR-1999			WOODSR
OC RECOMMENDATION	11-MAR-1999		WITHHOLD	WOODSR
			EIR REVIEW-CONCUR W/DISTRICT	
ASSIGNED INSPECTION	02-JUN-1999 PS			SDELLAFA
INSPECTION PERFORMED	18-JUN-1999	17-JUN-1999		SDELLAFA
DO RECOMMENDATION	18-JUN-1999		WITHHOLD	SDELLAFA
			BPC PROCESS VALIDATION INADEQUATE LAB CONTROLS	

NEW JERSEY DISTRICT CONTINUES TO RECOMMEND WITHHOLD FOR THIS APPLICATION AFTER A RE-INSPECTION. THE PROCESS HAS NOT BEEN DEMONSTRATED TO BE CONSISTENT AND LAB CONTROLS ARE INADQUATE.

EIR RECEIVED BY OC	28-JUN-1999			HARTMANB
OC RECOMMENDATION	28-JUN-1999		WITHHOLD	HARTMANB
			EIR REVIEW-CONCUR W/DISTRICT	
SUBMITTED TO DO	21-SEP-1999 GMP			EGASM
ASSIGNED INSPECTION	07-OCT-1999 PS			RBROWN4
DO RECOMMENDATION	19-OCT-1999		WITHHOLD	RBROWN4
			FIRM NOT READY	

FIRM HAS REQUESTED AT LEAST A SIX WEEK DELAY IN ORDER TO QUALUIFY PH PROBES USED DURING DS MANUFACTURE.

OC RECOMMENDATION	02-NOV-1999		WITHHOLD	EGASM
			FIRM NOT READY	
ASSIGNED INSPECTION	16-DEC-1999 PS			RBROWN4
INSPECTION PERFORMED	08-MAR-2000	24-FEB-2000		RBROWN4
EIR RECEIVED BY OC	14-MAR-2000			ALCOCKP
DO RECOMMENDATION	13-APR-2000		WITHHOLD	RBROWN4
			CONTROL COMP, INTERMED, RAW MA	

NWJ-PAI SHOWED [redacted] NOT ADEQUATE AND PARTS OF [redacted] BATCHES HAVE FAILED WITH HIGH IMPURITY WHEN TEMP RANGE HAS NOT BEEN MAINTAINED. ALSO, THE IP TESTS USED TO ESTIMATE IMP. AMOUNTS IN THE ARE NOT VALIDATED. IN ADDITION CHROMATOGRAPHIC DATA WAS ROUTINELY DISCARDED AT THIS FIRM.

OC RECOMMENDATION	19-MAY-2000		ACCEPTABLE	ALCOCKP
			FIRM RESPONSE TO DEFIC. ADEQUA	

EIR RECEIVED ON 3/17/00 - REVIEW CONDUCTED BY EDWIN RIVERA ON 3/21/00 WITH A RECOMMENDATION TO CONCUR WITH DISTRICT EIR RECOMMENDATION (VAI) AND ADEQUATE CORRECTIVE ACTIONS AS INDICATED IN FIRM'S RESPONSE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: NDA 21078/000
Stamp: 30-DEC-1998 Regulatory Due: 30-JUN-1999
Applicant: GLAXO WELLCOME
5 MOORE DR
RESEARCH TRIANGLE PARK, NC 27

Priority: 4P Org Code: 590
Action Goal: District Goal: 01-MAY-1999
Brand Name: MALARONE (ATOVAQUONE/PROGUANIL HCL) TABL
Established Name:
Generic Name: ATOVAQUONE/PROGUANIL HCL
Dosage Form: TAB (TABLET)
Strength: 250/100 MG, 62.5/25 MG

FDA Contacts:
M. DEMPSEY (HFD-590) 301-827-2127 , Project Manager
J. SMITH (HFD-590) 301-827-2175 , Review Chemist
N. SCHMUFF (HFD-590) 301-827-2425 , Team Leader

Overall Recommendation:

WITHHOLD on 28-JUN-1999 by B. HARTMAN (HFD-324) 301-827-0067
WITHHOLD on 11-MAR-1999 by R. WOODS (HFD-324) 301-827-0062

Establishment: 9610411
GLAXO OPERATIONS UK LTD
PRIORY ST
WARE, HERTFORDSHIRE, UK

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 12-JAN-1999
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: FINISHED DOSAGE OTHER TESTER

Establishment: 9615283
GLAXO WELLCOME INC
7333 MISSISSAUGA RD. NORTH
MISSISSAUGA, ONTARIO, CA L5N 6I

DMF No:
AADA No:

Profile: TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 27-JAN-1999
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Establishment: 9610414
GLAXO WELLCOME OPERATIONS L
WELLCOME FNDTN TEMPLE HILL
DARTFORD, KENT, UK DA1 5AH

DMF No:
AADA No:

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Profile: CSN OAI Status: NONE Responsibilities: DRUG SUBSTANCE
Last Milestone: OC RECOMMENDATION MANUFACTURER
Milestone Date: 05-FEB-1999 FINISHED DOSAGE OTHER TESTER
Decision: ACCEPTABLE
Reason: BASED ON PROFILE
Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 27-JAN-1999
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: [redacted] DMF No: [redacted]
AADA No:

Profile: CSN OAI Status: POTENTIAL OAI Responsibilities: [redacted]
Last Milestone: OC RECOMMENDATION
Milestone Date: 28-JUN-1999
Decision: WITHHOLD
Reason: EIR REVIEW-CONCUR W/DISTRICT