

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-268

CHEMISTRY REVIEW(S)

NDA 22-268

**Coartem (artemether/lumefantrine) Tablets,
20 mg/120 mg**

Novartis Pharmaceuticals Corporation

**Shrikant Pagay, Dorota Matecka
Division of Pre-Marketing Assessment II, Branch IV
ONDQA**

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Chemistry Review Data Sheet

1. NDA 22-268
2. REVIEW #: 3
3. REVIEW DATE: 23-Mar-2009
4. REVIEWERS: Shrikant Pagay, Dorota Matecka
5. PREVIOUS DOCUMENTS:

| <u>Submission(s) Reviewed</u> | <u>Document Date</u> |
|--|----------------------|
| Original (Drug Substance) | 15-May-2008 |
| Original (Drug Product) | 26-Jun-2008 |
| IR (DS facilities IR) | 14-Aug-2008 |
| IR (package samples and DP methods request) | 28-Aug-2008 |
| BC (DS facilities response) | 28-Aug-2008 |
| IR (74-Day Letter) | 08-Sep-2008 |
| BC (package samples response) | 12-Sep-2008 |
| BC (response to DP methods validation) | 15-Sep-2008 |
| BC (response to 74-Day letter) | 16-Sep-2008 |
| BC (DP stability update) | 19-Sep-2008 |
| BC (response to 10/01/08 telecon pharm/tox request) | 08-Oct-1008 |
| IR (DS/DP IR; sent previously by e-mail dated 23-Sep-2008) | 09-Oct-2008 |
| Teleconference | 21-Oct-2008 |
| IR (DS/DP IR) | 28-Oct-2008 |
| IR (second pharm/tox request by fax) | 28-Oct-2008 |
| Teleconference | 28-Oct-2008 |
| BC (response to question 12) | 31-Oct-2008 |
| BC (response to 10/28/08 IR) | 05-Nov-2008 |
| BC (response to pharm/tox IR dated 10/28/08) | 05-Nov-2008 |
| BC (response to 10/09/08 IR) | 06-Nov-2008 |
| IR (previously sent by e-mail dated 21-Nov-2008) | 26-Nov-2008 |
| BC (response to 11/26/08 IR) | 04-Dec-2008 |

Chemistry Review Data Sheet

| | |
|------------------------------|-------------|
| BC | 16-Dec-2008 |
| BC | 22-Dec-2008 |
| IR | 05-Mar-2009 |
| BC (response to 03/05/09 IR) | 11-Mar-2009 |
| IR | 17-Mar-2009 |
| BC (response to 03/17/09 IR) | 18-Mar-2009 |

6. SUBMISSION(S) BEING REVIEWED:

| <u>Submission(s) Reviewed</u> | <u>Document Date</u> |
|-------------------------------|----------------------|
| BC | 16-Dec-2008 |
| BC | 22-Dec-2008 |
| BC (response to 03/05/09 IR) | 11-Mar-2009 |
| BC (response to 03/17/09 IR) | 18-Mar-2009 |

7. NAME & ADDRESS OF APPLICANT:

| | |
|-----------------|--------------------------------------|
| Name: | Novartis Pharmaceuticals Corporation |
| Address: | One Health Plaza |
| Representative: | James L. DeMartino, Ph.D. |
| Telephone: | (862) 778-2645 |

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: COARTEM
- b) Non-Proprietary Name (USAN): artemether and lumefantrine
- c) Code Name/#: COA566A
- d) Chem. Type/Submission Priority:
 - Chem. Type: 1
 - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Antimalarial

Chemistry Review Data Sheet

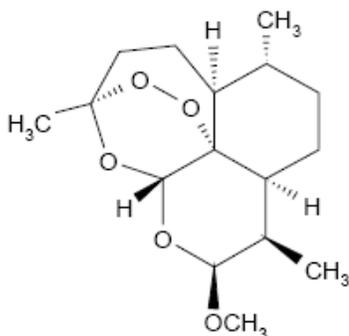
11. DOSAGE FORM: Tablets
12. STRENGTH/POTENCY: 20 mg artemether and 120 mg lumefantrine
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: Rx OTC
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):
 SPOTS product – Form Completed
 Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

ArtemetherChemical name:

[3R-(3 α , 5 α β , 6 β , 8 α β , 9 α , 10 α , 12 β -12aR)]-Decahydro-10-methoxy-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzo-dioxepine

Molecular Formula: C₁₆H₂₆O₅

Molecular Weight: 298.38

Structure:

Chemistry Review Data Sheet

Lumefantrine

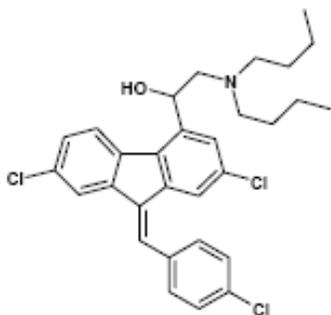
Chemical name:

(±)-2-Dibutylamino-1-[2,7-dichloro-9-(4-chlorobenzylidene)-9H-fluoren-4-yl]ethanol

Molecular formula: C₃₀H₃₂Cl₃NO

Molecular weight: 528.95

Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE ¹ | STATUS ² | DATE REVIEW COMPLETED | COMMENTS |
|---------|------|---------|-----------------|-------------------|---------------------|-----------------------|----------|
| (b) (4) | III | (b) (4) | [REDACTED] | 4 | N/A | | |
| | III | (b) (4) | [REDACTED] | 4 | N/A | | |
| | III | (b) (4) | [REDACTED] | 4 | N/A | | |
| | III | (b) (4) | [REDACTED] | 4 | N/A | | |
| | III | (b) (4) | [REDACTED] | 4 | N/A | | |
| | III | (b) (4) | [REDACTED] | 4 | N/A | | |
| | III | (b) (4) | [REDACTED] | 4 | N/A | | |
| | III | (b) (4) | [REDACTED] | 4 | N/A | | |

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

Chemistry Review Data Sheet

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: N/A

18. STATUS:

| CONSULTS | RECOMMENDATION | DATE | REVIEWER |
|--------------------|---|-------------|--------------------|
| Biometrics | N/A | | |
| EES | Acceptable | 27-Mar-2009 | E. Johnson |
| Pharm/Tox | Acceptable (see Review Notes) | 22-Dec-2008 | Dr. William Taylor |
| Biopharm | N/A | | |
| LNC | N/A | | |
| Methods Validation | N/A | | |
| DMEPA | Acceptable (name COARTEM) | 11-Nov-2008 | Denise Baugh |
| EA | N/A (request for a categorical exclusion) | | |
| Microbiology | N/A | | |

Appears This Way On Original

The Chemistry Review for NDA 22-268

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is recommended for approval with a post-marketing requirement and a post-marketing commitment (described below).

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

1. Post-Marketing Requirement (PMR):

Conduct spectral characterization of all specified impurities of both drug substances, i.e. artemether impurities (b) (4) and lumefantrine impurities (b) (4)

2. Post-Marketing Commitment (PMC):

Develop a dissolution test method for Coartem Tablets to achieve a minimum (b) (4) dissolution of each component, artemether and lumefantrine.

II. Summary of Chemistry Assessments

This is a CMC Review # 3 of this NDA, which addresses additional issues pertaining to both drug substances and the drug product, including the status of manufacturing facilities. This review was conducted by Shrikant Pagay and Dorota Matecka.

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

Coartem (artemether 20 mg and lumefantrine 120 mg tablet) was first developed in mid 1990s under World Health Organization (WHO) program to control tropical diseases. Coartem is registered under a different trade name and marketed outside US. Therefore, there is considerable manufacturing and controls history for this drug.

Coartem Tablets (COA566A) as submitted via this NDA, contain two drug substances, artemether and lumefantrine, both of which are new molecular entities.

The artemether drug substance, is a semi-synthetic moiety that is synthesized from the (b) (4) starting material. (b) (4) is an antimalarial agent extracted from the leaves of *Artemisia annua L.* Artemether is a methyl ether derivative of dihydroartemisinin. The latter is derived from (b) (4) through the reduction of the lactone functionality. The acidic methylation of hemi-acetal dihydroartemisinin in the synthesis of artemether drug substance

Executive Summary Section

favors the β -anomeric form of artemether. Artemether is a white to slightly yellow, crystalline powder with a melting point of 86°-90°C and specific rotation of +166° to +173°. Artemether is freely soluble in acetone, soluble in methanol and ethanol, and practically insoluble in water. Artemether is an optically active molecule and contains eight asymmetric centers, seven of them are set from the naturally occurring starting material, (b) (4). There are two known polymorphs of artemether (Polymorphs A and B). Polymorph A, the stable species at room temperature, was chosen for pharmaceutical application. The quality of the artemether drug substance is controlled through a set of appropriate tests and acceptance criteria, including identity, assay, impurities, particle size, microbial limits, and residual solvents. Artemether has been shown stable through 12 months when stored at 5° ± 3°C.

The lumefantrine drug substance, is a synthetic moiety that is obtained in a (b) (4) -step synthesis starting from (b) (4) procedures to obtain final drug substance. Lumefantrine is a yellow, crystalline powder with a melting point of 128° - 132°C. Lumefantrine is freely soluble in DMF, chloroform and ethyl acetate, soluble in dichloromethane, slightly soluble in ethanol and methanol, and insoluble in water. Lumefantrine has one chiral center; the lumefantrine drug substance is isolated as a racemic mixture. Only one polymorphic form has been identified for lumefantrine. The quality of the lumefantrine drug substance is controlled through a set of appropriate tests and acceptance criteria, including identity, assay, impurities, particle size, microbial limits, and residual solvents. Lumefantrine drug substance has been shown stable at room temperature.

The proposed drug product, Coartem Tablet, is a fixed combination of two antimalarial drugs, artemether and lumefantrine. Each tablet contains 20 mg of artemether and 120 mg of lumefantrine for oral drug delivery. The tablets are yellow, round flat with beveled edges and score on one side. The light yellow color of the tablet is due to lumefantrine. For identification, the tablets are printed on the scored side of the tablet with N/C and on the other side of the tablet with CG; per applicant's statement, these identification marks do not have any specific meaning. The total tablet weight is 240 mg. The tablet components besides the active drugs are microcrystalline cellulose, croscarmellose cellulose, hypromellose (b) (4) colloidal silicon dioxide, polysorbate 80, magnesium stearate (b) (4). All inactive components meet USP/NF/Ph Eur quality standards. The tablets are packaged in (b) (4) bottles with child resistant closures and induction seals, and in (b) (4) blisters with push thru aluminum lidding foil backing.

(b) (4)

Artemether is slightly soluble in water and lumefantrine is insoluble. However, both drugs are highly lipophilic favoring better absorption if promptly dissolved in the GI tract. The proposed dissolution specifications, especially that of artemether with Q values (% dissolved specification (b) (4) dissolved in (b) (4) and (b) (4) in (b) (4)) are not satisfactory; the method

Executive Summary Section

needs to be revised to achieve dissolution specification at $Q=(b)(4)$ to insure consistent quality attribute. The dissolution test is primarily a quality control test since there has been no attempt to develop an IV/IVC. All clinical/PK data shows that both drugs are available systemically. However, no data were provided to demonstrate if the proposed tablet formulation is optimally bioavailable.

The submission has included stability data on approximately $(b)(4)$ production scale batches with data through the proposed shelf life. Multiple analytical testing procedures are proposed for the identification, dissolution, assay, impurities, and content uniformity to demonstrate that the tablet quality is robust, however, some test methods, specifically the thin layer chromatographic method (TLC) for artemether degradation products (impurities) could be considered semi-quantitative. The sponsor has been encouraged to develop a more quantitative method. The proposed shelf life of 24 months is acceptable.

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

A single tablet containing 20 mg artemether and 120 mg lumefantrine has been developed for oral administration for the treatment of acute uncomplicated malaria due to infections with *Plasmodium falciparum* $(b)(4)$

Coartem tablets should be taken with food. The adult dose is 4 tablets twice a day for 3 days, i.e., a total of 24 tablets administered over 3 days. It is important that each dose is administered as per set schedule as follows: Take 4 tablets followed by second dose of another 4 tablets after 8 hours on day 1; on second and third day each take 4 tablets in the morning and 4 in the evening. The pediatric dose varies with the body weight ranging from 1, 2 or 3 tablets twice daily for 3 days. If the tablets are hard to swallow, crush the tablet in a clean cup with 1 to 2 teaspoonfuls of water. If necessary, rinse the cup with water to take the entire dose. The dosing should always be followed with food and/or drink such as milk. The line separating the letters N and C on one side of the tablets is not meant as a break line to achieve divisibility of the tablets for an equally divided dose. In view of the administration of four tablets per standard dose for adults and of one, two or three tablets per dose for children there is no obvious need to divide the tablets other than breaking them for more convenient administration.

C. Basis for Approvability or Not-Approval Recommendation

This NDA has provided sufficient information to assure identity, strength, purity, and quality of both drug substances and the drug product. Several remaining issues have been resolved satisfactorily since CMC Review # 2.

A recommendation regarding the qualification of the proposed acceptance criteria for impurities have been obtained from the pharm/tox review team for this NDA. Per this recommendation (attached in the of this review), the applicant can market the batches of Coartem with the proposed acceptance; however, additional post-approval studies (specifically in vitro bacterial mutation assay) will be required to qualify these levels. This recommendation will be included in the action letter as one of the Post-Marketing Requirements (PMR) for this NDA. In addition, a chemistry recommendation was conveyed to the applicant to conduct spectral characterization of all specified impurities of both drug substances, i.e. artemether impurities $(b)(4)$ and lumefantrine impurities $(b)(4)$

Executive Summary Section

which will also be included in the action letter for this NDA as one of the PMRs. Based on the currently available data, the proposed acceptance criteria for two of the impurities^{(b) (4)}

_____ were tightened. These acceptance criteria may be further revised post-approval when the results of in vitro bacterial mutation assay become available. In addition, the applicant has committed to develop an HPLC procedure that would detect and quantify all impurities in both drug substances and the drug product. The applicant has also agreed to develop a dissolution test method to achieve^{(b) (4)} dissolution of each component in Coartem Tablets, artemether and lumefantrine, through the proposed shelf life, which will be listed as one of the Post-Marketing Commitments (PMC) in the action letter for this NDA.

All manufacturing facilities involved in the manufacturing, packaging and testing of both drug substances and the drug product via this NDA are now acceptable; an overall acceptable recommendation was made by the Office of Compliance on 27-Mar-2009 (a copy of EER has been attached in the end of this review).

The proposed trade name, COARTEM, was found acceptable by DMEPA. The proposed labeling and the container, and carton labels were found acceptable.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistNames/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

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

/s/

Dorota Matecka
3/30/2009 10:52:52 AM
CHEMIST

Norman Schmuiff
3/30/2009 02:03:30 PM
CHEMIST

NDA 22-268

**Coartem (artemether/lumefantrine) Tablets,
20 mg/120 mg**

Novartis Pharmaceuticals Corporation

**Shrikant Pagay, Dorota Matecka
Division of Pre-Marketing Assessment II, Branch IV
ONDQA**

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| B. Description of How the Drug Product is Intended to be Used..... | 10 |
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| III. Administrative..... | 11 |
| A. Reviewer's Signature..... | 11 |
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| C. CC Block | 11 |
| Chemistry Assessment | 12 |

Chemistry Review Data Sheet

1. NDA 22-268
2. REVIEW #: 2
3. REVIEW DATE: 15-Dec-2008
4. REVIEWERS: Shrikant Pagay, Dorota Matecka
5. PREVIOUS DOCUMENTS:

| <u>Submission(s) Reviewed</u> | <u>Document Date</u> |
|--|----------------------|
| Original (Drug Substance) | 15-May-2008 |
| Original (Drug Product) | 26-Jun-2008 |
| IR (DS facilities IR) | 14-Aug-2008 |
| IR (package samples and DP methods request) | 28-Aug-2008 |
| BC (DS facilities response) | 28-Aug-2008 |
| IR (74-Day Letter) | 08-Sep-2008 |
| BC (package samples response) | 12-Sep-2008 |
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| BC (response to 74-Day letter) | 16-Sep-2008 |
| BC (DP stability update) | 19-Sep-2008 |
| BC (response to 10/01/08 telecon pharm/tox request) | 08-Oct-1008 |
| IR (DS/DP IR; sent previously by e-mail dated 23-Sep-2008) | 09-Oct-2008 |
| Teleconference | 21-Oct-2008 |
| IR (DS/DP IR) | 28-Oct-2008 |
| IR (second pharm/tox request by fax) | 28-Oct-2008 |
| Teleconference | 28-Oct-2008 |
| BC (response to question 12) | 31-Oct-2008 |
| BC (response to 10/28/08 IR) | 05-Nov-2008 |
| BC (response to pharm/tox IR dated 10/28/08) | 05-Nov-2008 |
| BC (response to 10/09/08 IR) | 06-Nov-2008 |
| IR (previously sent by e-mail dated 21-Nov-2008) | 26-Nov-2008 |
| BC (response to 11/26/08 IR) | 04-Dec-2008 |

Chemistry Review Data Sheet

6. SUBMISSION(S) BEING REVIEWED:

| <u>Submission(s) Reviewed</u> | <u>Document Date</u> |
|--|----------------------|
| Original (Drug Substance) | 15-May-2008 |
| Original (Drug Product) | 26-Jun-2008 |
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| BC (response to 10/09/08 IR) | 06-Nov-2008 |
| BC (response to 11/26/08 IR) | 04-Dec-2008 |

7. NAME & ADDRESS OF APPLICANT:

| | |
|-----------------|--------------------------------------|
| Name: | Novartis Pharmaceuticals Corporation |
| Address: | One Health Plaza |
| Representative: | James L. DeMartino, Ph.D. |
| Telephone: | (862) 778-2645 |

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: COARTEM
- b) Non-Proprietary Name (INN): artemether and lumefantrine (note: application process for the USAN names is pending)
- c) Code Name/#: COA566A
- d) Chem. Type/Submission Priority:
 - Chem. Type: 1
 - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION:

Chemistry Review Data Sheet

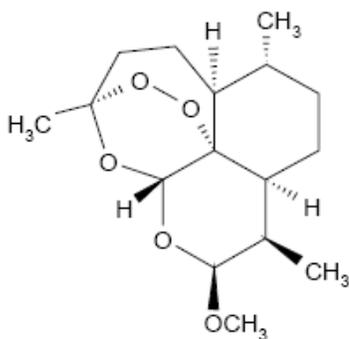
10. PHARMACOL. CATEGORY: Antimalarial
11. DOSAGE FORM: Tablets
12. STRENGTH/POTENCY: 20 mg artemether and 120 mg lumefantrine
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: Rx OTC
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):
 SPOTS product – Form Completed
 Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

ArtemetherChemical name:

[3R-(3 α , 5 α β , 6 β , 8 α β , 9 α , 10 α , 12 β -12 α R)]-Decahydro-10-methoxy-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzo-dioxepin

Molecular Formula: C₁₆H₂₆O₅

Molecular Weight: 298.38

Structure:

Chemistry Review Data Sheet

Lumefantrine

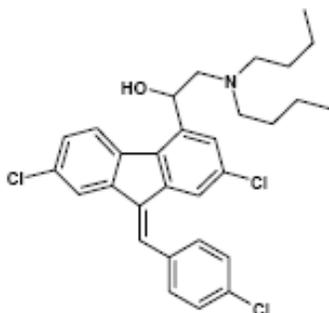
Chemical name:

(±)-2-Dibutylamino-1-[2,7-dichloro-9-(4-chlorobenzylidene)-9H-fluoren-4-yl]ethanol

Molecular formula: C₃₀H₃₂Cl₃NO

Molecular weight: 528.95

Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE ¹ | STATUS ² | DATE REVIEW COMPLETED | COMMENTS |
|---------|------|---------|-----------------|-------------------|---------------------|-----------------------|----------|
| (b) (4) | III | (b) (4) | (b) (4) | 4 | N/A | | |
| (b) (4) | III | (b) (4) | (b) (4) | 4 | N/A | | |
| (b) (4) | III | (b) (4) | (b) (4) | 4 | N/A | | |
| (b) (4) | III | (b) (4) | (b) (4) | 4 | N/A | | |
| (b) (4) | III | (b) (4) | (b) (4) | 4 | N/A | | |
| (b) (4) | III | (b) (4) | (b) (4) | 4 | N/A | | |
| (b) (4) | III | (b) (4) | (b) (4) | 4 | N/A | | |
| (b) (4) | III | (b) (4) | (b) (4) | 4 | N/A | | |

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

Chemistry Review Data Sheet

- 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: N/A

18. STATUS:

| CONSULTS | RECOMMENDATION | DATE | REVIEWER |
|--------------------|---|-----------|--------------|
| Biometrics | N/A | | |
| EES | Pending | | |
| Pharm/Tox | Pending | | |
| Biopharm | N/A | | |
| LNC | N/A | | |
| Methods Validation | N/A | | |
| DMEPA | Acceptable (name COARTEM) | 11-Nov-08 | Denise Baugh |
| EA | N/A (request for a categorical exclusion) | | |
| Microbiology | N/A | | |

Appears This Way On Original

The Chemistry Review for NDA 22-268

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. However, labeling issues are still pending and a recommendation from the Office of Compliance on the site acceptability has not been made as of the date of this review. Therefore, from the CMC perspective, this NDA is not recommended for approval until all issues are resolved.

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

II. Summary of Chemistry Assessments

This is the second review of this NDA that addresses additional issues pertaining to both drug substances and the drug product, including the status of manufacturing facilities. This review was conducted by Dorota Matecka and Shrikant Pagay.

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

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The artemether drug substance, is a semi-synthetic moiety that is synthesized from the (b) (4) starting material. (b) (4) is an antimalarial agent extracted from the leaves of *Artemisia annua L.* Artemether is a methyl ether derivative of dihydroartemisinin. The latter is derived from artemisinin through the reduction of the lactone functionality. The acidic methylation of hemi-acetal dihydroartemisinin in the synthesis of artemether drug substance favors the β -anomeric form of artemether. Artemether is a white to slightly yellow, crystalline powder with a melting point of 86°-90°C and specific rotation of +166° to +173°. Artemether is freely soluble in acetone, soluble in methanol and ethanol, and practically insoluble in water. Artemether is an optically active molecule and contains eight asymmetric centers, seven of them are set from the naturally occurring starting material (b) (4). There are two known polymorphs of artemether (Polymorphs A and B). Polymorph A, the stable species at room temperature, was chosen for pharmaceutical application. The quality of the artemether drug substance is controlled through a set of appropriate tests and acceptance criteria, including

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identity, assay, impurities, particle size, microbial limits, and residual solvents. Artemether has been shown stable through 12 months when stored at $5^{\circ} \pm 3^{\circ}\text{C}$.

The lumefantrine drug substance, is a synthetic moiety that is obtained in a (b) (4) -step synthesis starting from (b) (4)

(b) (4) procedures to obtain final drug substance. Lumefantrine is a yellow, crystalline powder with a melting point of $128^{\circ} - 132^{\circ}\text{C}$. Lumefantrine is freely soluble in DMF, chloroform and ethyl acetate, soluble in dichloromethane, slightly soluble in ethanol and methanol, and insoluble in water. Lumefantrine has one chiral center; the lumefantrine drug substance is isolated as a racemic mixture. Only one polymorphic form has been identified for lumefantrine. The quality of the lumefantrine drug substance is controlled through a set of appropriate tests and acceptance criteria, including identity, assay, impurities, particle size, microbial limits, and residual solvents. Lumefantrine drug substance has been shown stable at room temperature.

The proposed drug product, Coartem Tablet, is a fixed combination of two antimalarial drugs, artemether and lumefantrine. Each tablet contains 20 mg of artemether and 120 mg of lumefantrine for oral drug delivery. The tablets are yellow, round flat with beveled edges and score on one side. The light yellow color of the tablet is due to lumefantrine. For identification, the tablets are printed on the scored side of the tablet with N/C and on the other side of the tablet with CG. The total tablet weight is 240 mg. The tablet components besides the active drugs are microcrystalline cellulose, croscarmellose cellulose, hypromellose (b) (4) colloidal silicon dioxide, polysorbate 80, magnesium stearate (b) (4). All inactive components meet USP/NF/Ph Eur quality standards. The tablets are packaged in (b) (4) bottles with child resistant closures and induction seals, and in (b) (4) blisters with push thru aluminum lidding foil backing.

(b) (4)

Artemether is slightly soluble in water and lumefantrine is insoluble. However, both drugs are highly lipophilic favoring better absorption if promptly dissolved in the GI tract. The proposed dissolution specifications, especially that of artemether with Q values (% dissolved specification = (b) (4) dissolved in (b) (4) and (b) (4) in (b) (4)) are not satisfactory; the method needs to be revised to achieve dissolution specification at $Q=(b) (4)$ to insure consistent quality attribute. The dissolution test is primarily a quality control test since no information is available in the submission for relative or absolute bioavailability of the two drugs or that of the proposed formulation. All clinical/PK data supports that both drugs artemether and lumefantrine are available systemically. However, no data were provided to demonstrate if the proposed tablet formulation is optimally bioavailable.

The submission has included stability data on approximately (b) (4) production scale batches with data through the proposed shelf life. Multiple analytical testing procedures are proposed for the

Executive Summary Section

identification, dissolution, assay, impurities, and content uniformity to demonstrate that the tablet quality is robust, however, some test methods, specifically the thin layer chromatographic method (TLC) for artemether degradation products (impurities) could be considered semi-quantitative. The sponsor has been encouraged to develop a more quantitative method. The proposed shelf life of 24 months is acceptable.

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

A single tablet containing 20 mg artemether and 120 mg lumefantrine has been developed for oral administration for the treatment of acute uncomplicated malaria due to infections with *Plasmodium falciparum* (b) (4).

Coartem tablets should be taken with food. The adult dose is 4 tablets twice a day for 3 days, i.e., a total of 24 tablets administered over 3 days. It is important that each dose is administered as per set schedule as follows: Take 4 tablets followed by second dose of another 4 tablets after 8 hours on day 1; on second and third day each take 4 tablets in the morning and 4 in the evening. The pediatric dose varies with the body weight ranging from 1, 2 or 3 tablets twice daily for 3 days. If the tablets are hard to swallow, crush the tablet in a clean cup with 1 to 2 teaspoonfuls of water. If necessary, rinse the cup with water to take the entire dose. The dosing should always be followed with food and/or drink such as milk.

C. Basis for Approvability or Not-Approval Recommendation

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. However, labeling issues are still pending and a recommendation from the Office of Compliance on the site acceptability has not been made as of the date of this review. Therefore, from the CMC perspective, this NDA is not recommended for approval until all issues are resolved.

There are ten manufacturing facilities involved in the manufacturing, packaging and testing of both drug substances and the drug product that have been included in the EER for this NDA. Six of those establishments (including the drug product manufacturer, Novartis, Suffern, NY, and one of the artemether drug substance manufacturers, (b) (4)) have been found acceptable by the Office of Compliance at this time. However, two facilities are currently under the OAI status (recommended for withhold). That includes (b) (4) which is one of the manufacturers of lumefantrine drug substance, and Novartis Ringaskiddy Pharma Ltd., Basel, Switzerland, which serves as one of testing facilities of both drug substances. In addition, two other facilities are scheduled for inspection in February, 2009 (including the manufacturer of the final lumefantrine intermediate and the second manufacturer of both drug substances; both facilities belonging to (b) (4), but located at different addresses).

The original application contains adequate chemistry manufacturing and controls information regarding the quality of both drug substances and the drug product. During the review, a number of comments requesting additional information were forwarded to the applicant and several issues relating to the manufacturing process, testing and specifications were resolved satisfactorily. The issue of qualification of the acceptance criteria for impurities have been discussed with the pharm/tox review team for this NDA. Per the recommendation included in the addendum to the pharm/tox review, the applicant can market the batches of Coartem with

Executive Summary Section

the proposed acceptance; however, additional post-approval toxicology studies (specifically in vitro bacterial mutation assay) may be recommended to qualify these levels. This recommendation may be included in the action letter as one of the post marketing commitment for this NDA.

The proposed trade name, COARTEM, was found acceptable by DMEPA. The proposed labeling and the container, and carton labels are under discussion with the applicant.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

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/s/

Dorota Matecka
12/15/2008 06:28:03 PM
CHEMIST

Norman Schmuft
12/18/2008 05:21:48 PM
CHEMIST

NDA 22-268

**Coartem (artemether/lumefantrine) Tablets,
20 mg/120 mg**

Novartis Pharmaceuticals Corporation

**Shrikant Pagay, Dorota Matecka
Division of Pre-Marketing Assessment II, Branch IV
ONDQA**

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1. NDA 22-268
2. REVIEW #: 1
3. REVIEW DATE: 24-Nov-2008
4. REVIEWERs: Shrikant Pagay, Dorota Matecka
5. PREVIOUS DOCUMENTS:

| <u>Submission(s) Reviewed</u> | <u>Document Date</u> |
|--|----------------------|
| Original (Drug Substance) | 15-May-2008 |
| Original (Drug Product) | 26-Jun-2008 |
| IR (DS facilities IR) | 14-Aug-2008 |
| IR (package samples and DP methods request) | 28-Aug-2008 |
| BC (DS facilities response) | 28-Aug-2008 |
| IR (74-Day Letter) | 08-Sep-2008 |
| BC (package samples response) | 12-Sep-2008 |
| BC (response to DP methods validation) | 15-Sep-2008 |
| BC (response to 74-Day letter) | 16-Sep-2008 |
| BC (DP stability update) | 19-Sep-2008 |
| BC (response to 10/01/08 telecon pharm/tox request) | 08-Oct-1008 |
| IR (DS/DP IR; sent previously by e-mail dated 23-Sep-2008) | 09-Oct-2008 |
| Teleconference | 21-Oct-2008 |
| IR (DS/DP IR) | 28-Oct-2008 |
| IR (second pharm/tox request by fax) | 28-Oct-2008 |
| Teleconference | 28-Oct-2008 |
| BC (response to question 12) | 31-Oct-2008 |
| BC (response to 10/28/08 IR) | 05-Nov-2008 |
| BC (response to pharm/tox IR dated 10/28/08) | 05-Nov-2008 |
| BC (response to 10/09/08 IR) | 06-Nov-2008 |
| IR | 24-Nov-2008 |

Chemistry Review Data Sheet

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|--|---------------|
| Original (Drug Substance) | 15-May-2008 |
| Original (Drug Product) | 26-Jun-2008 |
| BC (DS facilities response) | 28-Aug-2008 |
| BC (package samples response) | 12-Sep-2008 |
| BC (response to DP methods validation) | 15-Sep-2008 |
| BC (response to 74-Day letter) | 16-Sep-2008 |
| BC (DP stability update) | 19-Sep-2008 |
| BC (response to 10/01/08 telecon pharm/tox request) | 08-Oct-1008 |
| BC (response to question 12) | 31-Oct-2008 |
| BC (response to 10/28/08 IR) | 05-Nov-2008 |
| BC (response to pharm/tox IR dated 10/28/08) | 05-Nov-2008 |
| BC (response to 10/09/08 IR) | 06-Nov-2008 |

7. NAME & ADDRESS OF APPLICANT:

| | |
|-----------------|--------------------------------------|
| Name: | Novartis Pharmaceuticals Corporation |
| Address: | One Health Plaza |
| Representative: | James L. DeMartino, Ph.D. |
| Telephone: | (862) 778-2645 |

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: COARTEM
- b) Non-Proprietary Name (INN): artemether and lumefantrine (note: application process for the USAN names is pending)
- c) Code Name/#: COA566A
- d) Chem. Type/Submission Priority:
 - Chem. Type: 1
 - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION:

Chemistry Review Data Sheet

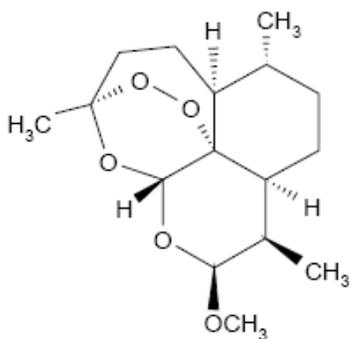
10. PHARMACOL. CATEGORY: Antimalarial
11. DOSAGE FORM: Tablets
12. STRENGTH/POTENCY: 20 mg artemether and 120 mg lumefantrine
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: Rx OTC
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):
 SPOTS product – Form Completed
 Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

ArtemetherChemical name:

[3R-(3 α , 5 $\alpha\beta$, 6 β , 8 $\alpha\beta$, 9 α , 10 α , 12 β -12aR)]-Decahydro-10-methoxy-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzo-dioxepin

Molecular Formula: C₁₆H₂₆O₅

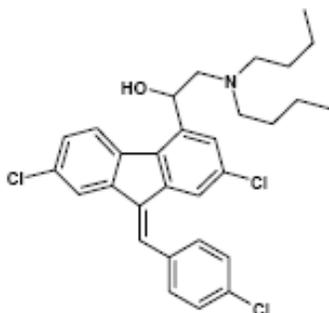
Molecular Weight: 298.38

Structure:

Chemistry Review Data Sheet

LumefantrineChemical name:

(±)-2-Dibutylamino-1-[2,7-dichloro-9-(4-chlorobenzylidene)-9H-fluoren-4-yl]ethanol

Molecular formula: C₃₀H₃₂Cl₃NOMolecular weight: 528.95Structure:

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE ¹ | STATUS ² | DATE REVIEW COMPLETED | COMMENTS |
|---------|------|---------|-----------------|-------------------|---------------------|-----------------------|----------|
| (b) (4) | III | (b) (4) | | 4 | N/A | | |
| | III | (b) (4) | | 4 | N/A | | |
| | III | (b) (4) | | 4 | N/A | | |
| | III | (b) (4) | | 4 | N/A | | |
| | III | (b) (4) | | 4 | N/A | | |
| | III | (b) (4) | | 4 | N/A | | |
| | III | (b) (4) | | 4 | N/A | | |
| | III | (b) (4) | | 4 | N/A | | |

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

Chemistry Review Data Sheet

- 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: N/A

18. STATUS:

| CONSULTS | RECOMMENDATION | DATE | REVIEWER |
|--------------------|---|------|----------|
| Biometrics | N/A | | |
| EES | Pending | | |
| Pharm/Tox | Pending | | |
| Biopharm | N/A | | |
| LNC | N/A | | |
| Methods Validation | N/A | | |
| DMEPA | Pending | | |
| EA | N/A (request for a categorical exclusion) | | |
| Microbiology | N/A | | |

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The Chemistry Review for NDA 22-268

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is not recommended for approval at this time. The overall compliance recommendation has not been completed by the Office of Compliance for this NDA. In addition, the issue of qualification of the proposed acceptance criteria for impurities listed in the drug substances and the drug product specifications is under internal discussion with the pharm/tox review team.

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

II. Summary of Chemistry Assessments

The review of this NDA was conducted by Dorota Matecka (both Drug Substance sections) and Shrikant Pagay (Drug Product section). The Drug Product review is placed in DFS as a separate document.

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

Coartem (artemether 20 mg and lumefantrine 120 mg tablet) was first developed in mid 1990s under World Health Organization (WHO) program to control tropical diseases. Coartem is registered under a different trade name and marketed outside US. Therefore, there is considerable manufacturing and controls history for this drug.

Coartem Tablets (COA566A) as submitted via this NDA, contain two drug substances, artemether and lumefantrine, both of which are new molecular entities.

The artemether drug substance, is a semi-synthetic moiety that is synthesized from the (b) (4) starting material. (b) (4) is an antimalarial agent extracted from the leaves of *Artemisia annua L.* Artemether is a methyl ether derivative of dihydroartemisinin. The latter is derived from artemisinin through the reduction of the lactone functionality. The acidic methylation of semi-acetal dihydroartemisinin in the synthesis of artemether drug substance favors the β -anomeric form of artemether. Artemether is a white to slightly yellow, crystalline powder with a melting point of 86°-90°C and specific rotation of +166° to +173°. Artemether is freely soluble in acetone, soluble in methanol and ethanol, and practically insoluble in water. Artemether is an optically active molecule and contains eight asymmetric centers, seven of them are set from the naturally occurring starting material, (b) (4). There are two known polymorphs of artemether (Polymorphs A and B). Polymorph A, the stable species at room temperature, was chosen for pharmaceutical application. The quality of the artemether drug

Executive Summary Section

substance is controlled through a set of appropriate tests and acceptance criteria, including identity, assay, impurities, particle size, microbial limits, and residual solvents. Artemether has been shown stable through 12 months when stored at $5^{\circ} \pm 3^{\circ}\text{C}$.

The lumefantrine drug substance, is a synthetic moiety that is obtained in a (b) (4) -step synthesis starting from (b) (4) procedures to obtain final drug substance. Lumefantrine is a yellow, crystalline powder with a melting point of $128^{\circ} - 132^{\circ}\text{C}$. Lumefantrine is freely soluble in DMF, chloroform and ethyl acetate, soluble in dichloromethane, slightly soluble in ethanol and methanol, and insoluble in water. Lumefantrine has one chiral center; the lumefantrine drug substance is isolated as a racemic mixture. Only one polymorphic form has been identified for lumefantrine. The quality of the lumefantrine drug substance is controlled through a set of appropriate tests and acceptance criteria, including identity, assay, impurities, particle size, microbial limits, and residual solvents. Lumefantrine drug substance has been shown stable at room temperature.

The proposed drug product, Coartem Tablet, is a fixed combination of two antimalarial drugs, artemether and lumefantrine. Each tablet contains 20 mg of artemether and 120 mg of lumefantrine for oral drug delivery. The tablets are yellow, round flat with beveled edges and score on one side. The light yellow color of the tablet is due to lumefantrine. For identification, the tablets are printed on the scored side of the tablet with N/C and on the other side of the tablet with CG. The total tablet weight is 240 mg. The tablet components besides the active drugs are microcrystalline cellulose, croscarmellose cellulose, hypromellose (b) (4) colloidal silicon dioxide, polysorbate 80, magnesium stearate (b) (4). All inactive components meet USP/NF/Ph Eur quality standards. The tablets are packaged in (b) (4) bottles with child resistant closures and induction seals, and in (b) (4) blisters with push thru aluminum lidding foil backing.

(b) (4)

Artemether is slightly soluble in water and lumefantrine is insoluble. However, both drugs are highly lipophilic favoring better absorption if promptly dissolved in the GI tract. The proposed dissolution specifications, especially that of artemether with Q values (% dissolved specification = (b) (4) dissolved in (b) (4) and (b) (4) in (b) (4)) are not satisfactory; the method needs to be revised to achieve dissolution specification at $Q=(b) (4)$ to insure consistent quality attribute. The dissolution test is primarily a quality control test since no information is available in the submission for relative or absolute bioavailability of the two drugs or that of the proposed formulation. All clinical/PK data supports that both drugs artemether and lumefantrine are available systemically. However, no data were provided to demonstrate if the proposed tablet formulation is optimally bioavailable.

Executive Summary Section

The submission has included stability data on approximately (b) (4) production scale batches with data through the proposed shelf life. Multiple analytical testing procedures are proposed for the identification, dissolution, assay, impurities, and content uniformity to demonstrate that the tablet quality is robust, however, some test methods, specifically the thin layer chromatographic method (TLC) for artemether degradation products (impurities) could be considered semi-quantitative. The sponsor will be encouraged to develop a more quantitative method. The proposed shelf life of 24 months is acceptable.

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

A single tablet containing 20 mg artemether and 120 mg lumefantrine has been developed for oral administration for the treatment of acute uncomplicated malaria due to infections with *Plasmodium falciparum* (b) (4).

Coartem tablets should be taken with food. The adult dose is 4 tablets twice a day for 3 days, i.e., a total of 24 tablets administered over 3 days. It is important that each dose is administered as per set schedule as follows: Take 4 tablets followed by second dose of another 4 tablets after 8 hours on day 1; on second and third day each take 4 tablets in the morning and 4 in the evening. The pediatric dose varies with the body weight ranging from 1, 2 or 3 tablets twice daily for 3 days. If the tablets are hard to swallow, crush the tablet in a clean cup with 1 to 2 teaspoonfuls of water. If necessary, rinse the cup with water to take the entire dose. The dosing should always be followed with food and/or drink such as milk.

C. Basis for Approvability or Not-Approval Recommendation

The application is not currently recommended for approval from the chemistry, manufacturing and controls point of view. There are two outstanding issues currently pending for this NDA; that includes the status of the manufacturing facilities and qualification of impurities.

As mentioned above, an overall compliance recommendation by the Office of Compliance has not been completed for this NDA at this point. Artemether drug substance is manufactured by two manufacturers, (b) (4). Lumefantrine drug substance is manufactured by two manufacturers, (b) (4). Upon approval, the drug product will be manufactured and marketed by Novartis. In addition, there are several other establishments involved in the milling and testing of both drug substances and the drug product. Two facilities, involved in the manufacture and testing of the drug product have been found acceptable. However, the status of other establishments is currently pending.

The original application contains mostly adequate chemistry manufacturing and controls information regarding the quality of both drug substances and the drug product. During the review, a number of comments requesting additional information were forwarded to the applicant and several issues relating to the manufacturing process, testing and specifications were resolved satisfactorily. However, there are several issues still pending resolution. These issues relate to the qualification of the proposed acceptance criteria for impurities listed in both drug substances and the drug product specifications. That includes several impurities of lumefantrine with structural alerts indicating a genotoxic potential, for which the currently proposed limits (set according to the ICH guidelines for any unspecified impurities) may not be appropriate. These issues are currently under discussion with the pharm/tox review team for this NDA.

Executive Summary Section

Other issues that will be further discussed with the applicant but are not approvability issues include stability commitment for annual batches of the drug substances, a currently proposed TLC method for artemether impurities and degradation products in the drug product and the currently proposed acceptance criteria for the drug product dissolution. In addition, several responses to the drug substance and the drug product comments received via recent NDA amendments need further clarification. These comments were forwarded to the applicant.

The proposed trade name, COARTEM, was found acceptable by DMEPA. The review of the proposed labeling and the container, and carton labels is pending.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

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/s/

Dorota Matecka
11/24/2008 07:37:07 PM
CHEMIST

Norman Schmuiff
11/24/2008 08:01:12 PM
CHEMIST

MEMORANDUM

Date: December 18, 2008

To: NDA 22-268

From: Elaine Morefield, Ph.D.
Division Director
Pre-marketing Assessment Division II
ONDQA

Subject: Tertiary review of ONDQA recommendation for NDA 22-268 Coartem (artemether/lumefantrine) Tablets 20mg/120mg.

I have assessed the ONDQA reviews of NDA 22-268, Coartem tablets. Adequate data, manufacturing process information and controls have been submitted to produce a quality product. There are still some outstanding CMC issues having to do with an impurity acceptance criteria and the overall Office of Compliance recommendation. These issues appear to be resolvable in the near future. ONDQA is not recommending approval from a CMC perspective until these issues are resolved. I concur with the ONDQA recommendation.

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/s/

Elaine Morefield
12/18/2008 04:13:07 PM
CHEMIST

NDA 22-268
(Drug Product review)

Coartem (artemether/lumefantrine) Tablets,
20 mg/120 mg

Novartis Pharmaceuticals Corporation

Shrikant Pagay, Dorota Matecka
Division of Pre-Marketing Assessment II, Branch IV
ONDQA

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This document contains only the Chemistry Assessment of the Drug Product section. For Chemistry Review Data Sheet see the first part of NDA 22-268 review (Drug Substance section).

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The Chemistry Review for NDA 22-268

The Executive Summary

This document contains only the Chemistry Assessment of the Drug Product section. For Executive Summary see the first part of NDA 22-268 review (Drug Substance section).

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Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

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/s/

Shrikant Pagay
11/24/2008 08:14:35 PM
CHEMIST
NDA 22268 Drug product review

Norman Schmuff
11/24/2008 09:09:53 PM
CHEMIST