

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20905

ADMINISTRATIVE DOCUMENTS

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA

DRAFT LABELING IS **NO LONGER** BEING SUPPLIED SO AS TO
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DISSEMINATED TO THE PUBLIC.

THIS SECTION
WAS
DETERMINED
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TO BE
RELEASABLE

21 pages

Hoechst Marion Roussel, Inc.
Patent Department

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26 February 1998

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
Park Bldg., Room 2-14
12420 Parktown Drive
Rockville, MD 20857

Subject Re: Original NDA Submission (20-905) for Lefunomide Tablets
Patent Information and Declaration

Dear Sir:

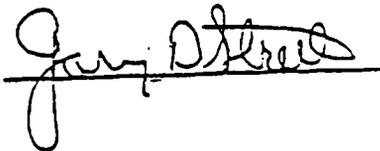
The undersigned submits that the following patent information is relevant to Lefunomide Tablets:

| | |
|---------------------|--|
| PATENT NUMBER(S): | United States Patent No. 5,679,709 |
| EXPIRATION DATE(S): | October 21, 2014 |
| PATENT OWNER: | Hoechst Aktiengesellschaft 65926 Frankfurt am Main Germany |
| TYPE OF PATENT: | Method of Use |

The undersigned declares that United States Patent No. 5,679,809 covers a metabolite of lefunomide and a method of using drug substance (lefunomide) and drug product (formulation) containing said drug substance in treating rheumatoid arthritis. United States Patent 5,679,709 has not been extended under 35USC156.

Two copies of this declaration are submitted herewith. Please list the above patent in the Orange Book Publication upon approval of the NDA.

Submitted by:



Gary D. Straet
Vice President
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Hoechst

Hoechst Marion Roussel
The Pharmaceutical Company of Hoechst

NDA 20-905
Leflunomide Tablets

CONFIDENTIAL
Hoechst Marion Roussel

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26 February 1998

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Food and Drug Administration
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12420 Parktown Drive
Rockville, MD 20857

Subject Re: Original NDA Submission (20-905) for Leflunomide Tablets
Patent Information and Declaration

Dear Sir:

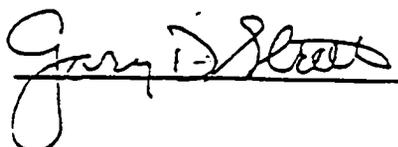
The undersigned submits that the following patent information is relevant to Leflunomide Tablets:

| | |
|---------------------|--|
| PATENT NUMBER(S): | United States Patent No. 4,351,341 |
| EXPIRATION DATE(S): | December 13, 1999, under the provisions of Uruguay Pact of the General Agreement on Tariffs and Trade ("GATT") |
| PATENT OWNER: | Hoechst Aktiengesellschaft 65926 Frankfurt am Main Germany |
| TYPE OF PATENT: | Drug Product (formulation) and Method of Use |

The undersigned declares that United States Patent No. 4,351,341 covers the drug product (formulation) containing the drug substance leflunomide and a method of using said drug substance and said drug product in treating rheumatoid arthritis. The patent has not been extended under 35USC156.

Two copies of this declaration are submitted herewith. Please list the above patent in the Orange Book Publication upon approval of the NDA.

Submitted by:


Gary D. Street
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Hoechst Marion Roussel
The Pharmaceutical Company of Hoechst

MARCH, 1998
HOECHST MARION ROUSSEL

13-3

Patent Information

NDA 20-905
Leflunomide Tablets

CONFIDENTIAL
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25 February 1998

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
Park Bldg., Room 2-14
12420 Parktown Drive
Rockville, MD 20857

Subject Re: Original NDA Submission (20-905) for Leflunomide Tablets
Patent Information and Declaration

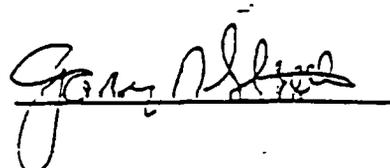
Dear Sir:

The undersigned submits that the following patent information is relevant to Leflunomide Tablets:

| | |
|---------------------|--|
| PATENT NUMBER(S): | United States Patent No. 4,284,786 |
| EXPIRATION DATE(S): | December 13, 1999, under the provisions of Uruguay Pact of the General Agreement on Tariffs and Trade ("GATT") |
| PATENT OWNER: | Hoechst Aktiengesellschaft 65926 Frankfurt am Main Germany |
| TYPE OF PATENT: | Drug Substance |

The undersigned declares that United States Patent No. 4,284,786 covers leflunomide, the drug substance of the drug product for which the above-referenced NDA is being submitted for approval for use in treating rheumatoid arthritis, and also covers both the drug product (formulation) containing the drug substance and methods of using said drug substance in treating rheumatoid arthritis. The patent has not been extended under 35USC156.

Two copies of this declaration are submitted herewith. Please list the above patent in the Orange Book Publication upon approval of the NDA.

Submitted by: 

Gary D. Street
Vice President
Hoechst Marion Roussel, Inc.
Patent Department

Hoechst

Hoechst Marion Roussel
The Pharmaceutical Company of Hoechst

EXCLUSIVITY SUMMARY for NDA #20-905 SUPPL # _____

Trade Name Arava Tablets

Generic Name Leflunomide 10 mg, 20 mg, and 100 mg

Applicant Name Hoechst Marion Roussel, Inc. HFD-550

Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it an original NDA?
YES /X/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /X/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /X/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /X/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 YEARS

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /X/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

**APPEARS THIS WAY
ON ORIGINAL**

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / / NO /X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____

NDA # _____

NDA # _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / / NO /X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____

NDA # _____

NDA # _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

**APPEARS THIS WAY
ON ORIGINAL**

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

- (2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

**APPEARS THIS WAY
ON ORIGINAL**

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

| | | |
|------------------|-------------|------------|
| Investigation #1 | YES / ___ / | NO / ___ / |
| Investigation #2 | YES / ___ / | NO / ___ / |
| Investigation #3 | YES / ___ / | NO / ___ / |

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
 NDA # _____ Study # _____
 NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

| | | |
|------------------|-------------|------------|
| Investigation #1 | YES / ___ / | NO / ___ / |
| Investigation #2 | YES / ___ / | NO / ___ / |
| Investigation #3 | YES / ___ / | NO / ___ / |

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
 NDA # _____ Study # _____
 NDA # _____ Study # _____

**APPEARS THIS WAY
ON ORIGINAL**

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_, Study # _____

Investigation #_, Study # _____

Investigation #_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # ___ YES / ___ / NO / ___ / Explain: _____

Investigation #2

IND # ___ YES / ___ / NO / ___ / Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES / ___ / Explain _____ NO / ___ / Explain _____

Investigation #2

YES / ___ / Explain _____ NO / ___ / Explain _____

- (c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / ___ / NO / ___ /

If yes, explain: _____

Signature 8/27/98
Date
Title: Project Manager

Signature of Division Director 9/10/98
Date

cc: Original NDA

Division File HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 20-905

Supplement # _____

Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-550 Trade (generic) name/dosage form: Arava (leflunomide tablet) Tablets
10 mg, 20 mg, and 100 mg.

Action: AP AE NA

Applicant Hoechst Marion Roussel

Therapeutic Class IP, Disease Modifying

Indication(s) previously approved None

Pediatric labeling of approved indication(s) is adequate _____ inadequate _____

Indication in this application Treatment of active rheumatoid arthritis to reduce signs and symptoms and to retard structural damage.
(For supplements, answer the following questions in relation to the proposed indication.)

- 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.
- 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.
 - a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.
 - b. The applicant has committed to doing such studies as will be required.
 - (1) Studies are ongoing,
 - (2) Protocols were submitted and approved.
 - (3) Protocols were submitted and are under review.
 - (4) If no protocol has been submitted, explain the status of discussions on the back of this form.
 - c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
- 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.
- 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

Signature of Preparer and Title Project Manager
(PM, CSO, MO, other)

8/27/98
Date

RA. 9/10/98

cc: Orig NDA/PLA # _____
HF _____ /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

Debarment Certification

Hoechst Marion Roussel, Inc. hereby certifies that we did not and will not use in any capacity the services of any person debarred under Section(a) or (b) in connection with this application.

Elaine Waller

Elaine Waller, PharmD
Vice President, North American
Regulatory Affairs

3/10/98

Date

**APPEARS THIS WAY
ON ORIGINAL**