CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-234

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Patent Certification

November 9, 2000

DICLOFENAC PATCH **NDA 21,234**

Institut Biochimique SA (IBSA) a Swiss corporation operated by Dr. Arturo Licenziati, plans to market Diclofenac Patch for treatment _____, and to that end has submitted a New Drug Application to the US Food and Drug Administration.

The drug, diclofenac epolamine, for treatment of pain using this topical formulation is the subject of US Patient 4,948,805.

Furthermore, Teikoku Seiyaku Co., Ltd., a Japanese corporation operated by Mr. Shozo Akazawa, is the manufacturer of this external anti-inflammatory and analgesic plaster preparation that is the subject of US Patient 5,607,690.

I certify that Institut Biochimique SA is entitled to market Diclofenac Patch for the above-mentioned indication, and to the best of my knowledge does not and will not infringe upon any current or pending US patents.

Signed:

Larry J Caldwell

Larry J. Caldwell, Ph.D.
US Representative of IBSA

November 9, 2000
Date

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3

NDA NUMBER
21-234

NAME OF APPLICANT / NDA HOLDER
Institut Biochimique SA (IBSA)

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Flector® Patch

ACTIVE INGREDIENT(S)	STRENGTH(S)
Hydroxy-2-ethyl)-1-Pyrrolidine Diclofenac Salt (DHEP)	1.3% w/w

DOSAGE FORM
Adhesive Patch

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e. one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,607,690	4/3/1997	4/13/2014

d. Name of Patent Owner
Teikoku Seiyaku Co. Ltd. & Altergon S.A.

Address *(of Patent Owner)*
567 Sanbonmatsu, Higashi-Kagawa

City/State
Kagawa, Japan

ZIP Code	FAX Number *(if available)*
769-2695	0081879/24-1555
Telephone Number	**E-Mail Address *(if available)***
0081879/25-2221	akazawa@teiyaku.co.jp

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address *(of agent or representative named in 1.e.)*

City/State

ZIP Code	FAX Number *(if available)*
Telephone Number	**E-Mail Address *(if available)***

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ **No**
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ **No**
4.2 Patent Claim Number *(as listed in the patent)* 4	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes	☒ **No**
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Dr. Arturo Licenziati, Managing Director	08/29/2006 9/5/2006

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name IBSA Institut Biochimique S.A	
Address Via del Piano	City/State Pambio-Noranco (Switzerland)
ZIP Code 6915	Telephone Number +41(0) 58 360 10 00
FAX Number *(if available)* +41(0) 58 360 16 55	E-Mail Address *(if available)* info@ibsa.ch

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

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NDA NUMBER
21-234

NAME OF APPLICANT / NDA HOLDER
Institut Biochimique SA (IBSA)

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Flector® Patch

ACTIVE INGREDIENT(S)	STRENGTH(S)
Hydroxy-2-ethyl)-1-Pyrrolidine Diclofenac Salt (DHEP)	1.3% w/w

DOSAGE FORM
Adhesive Patch

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1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
4,948,805	8/14/1990	08/14/2007

d. Name of Patent Owner
Altergon S.A. & Ricerfarma Srl

Address *(of Patent Owner)*
Altergon S.A. - Via Dogana Vecchia, 2

City/State
Lugano (Switzerland)

ZIP Code	FAX Number *(if available)*
6900	+41-91-9236862
Telephone Number	**E-Mail Address *(if available)***
+41-91-9227091	

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Clarence E. Jones Ph.D.

Address *(of agent or representative named in 1.e.)*
8602 Mossford Drive

City/State
Huntington Beach, CA

ZIP Code	FAX Number *(if available)*
92646	(714 (963-0078)
Telephone Number	**E-Mail Address *(if available)***
(714) 963-0078	cejtwsxx@verizon.net

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

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2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314 53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ **No**
4.2 Patent Claim Number *(as listed in the patent)* 4	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes	☒ **No**
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

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Dr. Arturo Licenziati, Managing Director	08/29/2006 9/5/2006

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Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
IBSA Institut Biochimique S.A.

Address	City/State
Via del Piano	Pambio-Noranco (Switzerland)
ZIP Code 6915	Telephone Number +41(0) 58 360 10 00
FAX Number *(if available)* +41(0) 58 360 16 55	E-Mail Address *(if available)* info@ibsa.ch

EXCLUSIVITY SUMMARY

NDA # 21-234 SUPPL # HFD # 170

Trade Name Flector Patch

Generic Name diclofenac epolamine topical patch 1.3%

Applicant Name IBSA

Approval Date, If Known January 31, 2007

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy 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 a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

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 ☒ 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 ☐ NO ☒

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

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

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 ☐

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

NDA#	20142	oral diclofenac potassium 50 mg (Cataflam)
NDA#	21005	diclofenac sodium topical gel 3% (Solaraze)
NDA#	20037	diclofenac sodium solution; opthalmic drops (Voltaren)
NDA#	19201	diclofenac sodium tablet, delayed-release 75 mg (Voltaren)
NDA#	20254	diclofenac sodium extended-release oral tablet, 100 mg (Voltaren XR)
NDA#	20607	diclofenac sodium; misoprostol delayed-release oral tablet 75 mg; 0.2 mg (Arthrotech)

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.)

X NA YES ☐ NO ☐

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. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs 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.

(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 ☐

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:

Protocol 05-05-98; Multi-Center, randomized study in parellel groups comparing efficacy and safety of Diclofenac Patch vs. placebo in the treatment of minor ankle sprains.

Protocol 00GB: A randomized, double-blind, placebo-controlled study of the efficacy and safety of diclofenac epolamine patch in minor soft tissue injury.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 ☒

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

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 ☒

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

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"):

Protocol 05-05-98; Multi-Center, randomized study in parellel groups comparing efficacy and safety of Diclofenac Patch vs. placebo in the treatment of minor ankle sprains.

Protocol 00GB: A randomized, double-blind, placebo-controlled study of the efficacy and safety of diclofenac epolamine patch in minor soft tissue injury.

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 ☒ ! NO ☐
Explain: ! Explain:
Foreign study conducted by applicant

Investigation #2 !
!
YES ☒ ! NO ☐
Explain: ! Explain:
Foreign study conducted by applicant

(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:

Name of person completing form: Lisa Basham
Title: Regulatory Project Manager
Date: 1-26-07

Name of Office/Division Director signing form: Bob Rappaport, MD
Title: Director, Division of Anesthesia, Analgesia and Rheumatology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Bob Rappaport
1/30/2007 06:09:12 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA # : 21234 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** _____

Stamp Date: December 18, 2000/AZ resubmission July 27, 2006 **PDUFA Goal Date:** January 31, 2007

HFD 170 **Trade and generic names/dosage form:** Flector Patch (diclofenac epolamine topical patch) 1.3%

Applicant: IBSA **Therapeutic Class:** NSAID

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- X Yes. Please proceed to the next question.
- ☐ No. PREA does not apply. Skip to signature block.

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) ***previously approved*** **(please complete this section for supplements only):** _____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: topical treatment of acute pain due to minor strains, sprains, and contusions

Is this an orphan indication?

- ☐ Yes. PREA does not apply. Skip to signature block.
- X No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.
- X No: Please check all that apply: X Partial Waiver X Deferred ____ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr._0____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._1____ Tanner Stage_____
Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- X **Other:** Topical NSAID patch not a practical approach to managing this indication in pediatric patients below the age of two.

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr.__2___ Tanner Stage_____
Max_____ kg_____ mo._____ yr.__16__ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- X **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): January 31, 2011

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is this an orphan indication?

- ☐ **Yes. PREA does not apply. Skip to signature block.**
- ☐ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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

/s/

Lisa Basham
1/31/2007 06:13:01 PM

Debarment Certification

November 9, 2000

DICLOFENAC PATCH **NDA 21,234**

In accordance with 21 U.S.C § 306 of the Federal Food, Drug and Cosmetic Act, this is to certify that no person, who has been or will be employed in connection with the development of Diclofenac Patch for [redacted] (IND 49-459, NDA 21-234), shall be disbarred.

Signed:

Larry J Caldwell

Larry J. Caldwell, Ph.D.
Study Director
US Representative of IBSA

November 9, 2000
Date

NDA 21-234
Diclofenac Epolamine Patch
IBSA Institut Biochimique SA

DEBARMENT CERTIFICATION

Pursuant to Section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, IBSA hereby certifies that:

IBSA did not and will not use in any capacity the services of any person debarred under subsection 306(a) or 306(b) in connection with its 505(b)(2) application for Diclofenac Epolamine Patch.

By: _____ Date: 8-24-06
Printed Name: Giuseppe Mautone
Title: Director R&D IBSA

By: _____ Date: 9/5/2006
Printed Name: Clarence Jones, Ph.D.
Title: Consultant to IBSA

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-234	Efficacy Supplement Type SE-	Supplement Number	
Drug: Diclofenac Epolamine Patch		Applicant: Institut Biochichimique SA	
RPM: Lisa Basham		HFD-170	Phone # 301-796-5214

Application Type: ( ) 505(b)(1) (X) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** ( ) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): Reference published literature only.

❖ Application Classifications:	
• Review priority	(X) Standard () Priority
• Chem class (NDAs only)	
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	January 31, 2007
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	(X) Paid UF ID number 4053
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No

• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	Yes
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) () Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	(X) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).* (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (3).* (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) Yes ( ) No ( ) Yes ( ) No ( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.* (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (5).* (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No ( ) Yes ( ) No
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	1/30/07 No
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	PM Reg Filing Rev 1/26/07

❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	NA 10/18/01
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	Approved, agreed upon labeling in approval letter
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DMETS 1/12/07
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	• NDA 20-998 (Celebrex) AP 12/15/06 • NDA 20-938/S-017 and NDA 21-530/S-005 (Mobic) AP 1/25/07
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	Approved, agreed upon labeling in approval letter
• Applicant proposed	
• Reviews	DMETS 1/12/07
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	PREA only
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	NA
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	6-6-98
• Pre-NDA meeting (indicate date)	2-1-00 and 3-28-00
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	NA

❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	DD 1/31/07 Clin TL 1/10/07
❖ Clinical review(s) *(indicate date for each review)*	1st cycle: 10/10/01 2nd cycle: 1/10/07
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	NA
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	NA
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	NA
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	1/31/07
❖ Demographic Worksheet *(NME approvals only)*	NA
❖ Statistical review(s) *(indicate date for each review)*	1st cycle: 9/21/01 2nd cycle: primary 1/12/07 2nd cycle TL:1/12/07
❖ Biopharmaceutical review(s) *(indicate date for each review)*	1st cycle: 10/4/01 2nd cycle: 1/22/07
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	NA
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	1st cycle: 10/11/01 2nd cycle: 1/23/07
• Bioequivalence studies	NA
❖ CMC review(s) *(indicate date for each review)*	1st cycle: 10/17/01 2nd cycle: 1/25/07
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	10/17/01
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	NA
❖ Facilities inspection (provide EER report)	Date completed: 8/29/06 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested (X) Not yet requested
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	1st cycle: 9/26/01 2nd cycle: 1/22/07
❖ Nonclinical inspection review summary	NA
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	NA
❖ CAC/ECAC report	NA

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

/s/

Lisa Basham
2/9/2007 02:01:02 PM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-234 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Flector® Patch
Established Name: Diclofenac Epolamine Patch 1.3%
Strengths:

Applicant: Institut Biochimique SA
Agent for Applicant (if applicable): Clarence E. Jones, PhD

Date of Application: July 27, 2006
Date of Receipt: July 31, 2006
Date clock started after UN:
Date of Planning Meeting: August 24, 2006
Filing Date: NA
Action Goal Date (optional): January 26, 2006 User Fee Goal Date: January 31, 2006

Indication(s) requested: Treatment of pain

Type of Original NDA: (b)(1) ☐ (b)(2) X
AND (if applicable)
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S ☐ P X
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 4s
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES X NO ☐

User Fee Status: Paid X Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☐ NO X
  If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO X

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO X
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES X NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES X NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES X NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐

2. This application is an eNDA or combined paper + eNDA YES X
   This application is: All electronic X Combined paper + eNDA ☐
   This application is in: NDA format X CTD format ☐
   Combined NDA and CTD formats ☐

   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES X NO ☐

   If an eNDA, all forms and certifications must be in paper and require a signature.

   If combined paper + eNDA, which parts of the application were submitted in electronic format?

   Additional comments:

3. This application is an eCTD NDA. YES ☐
   If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

   Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, _____ Years NO X
NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
YES ☒ NO ☐

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☒ NO ☐

- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☒ NO ☐

- PDUFA and Action Goal dates correct in tracking system? YES ☒ NO ☐
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 49,459

- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) 16 June 1998 NO ☐
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 28 March 2000 NO ☐
If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO ☒
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☐ NO X
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☐ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES X NO ☐

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES X NO ☐

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A X YES ☐ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A X YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA X YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☐ NO X
  If no, did applicant submit a complete environmental assessment? YES X NO ☐
  If EA submitted, consulted to EA officer, OPS? YES ☒ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐

- If a parenteral product, consulted to Microbiology Team? YES ☐ NO ☐

ATTACHMENT

MEMO OF PLANNING MEETING/Evaluation of Complete Response

DATE: August 24, 2006

NDA #: 21-234

DRUG NAMES: Diclofenac Epolamine Patch

APPLICANT: Institut Biochimique SA

BACKGROUND: This NDA is for a diclofenac epolamine (salt) Patch for the treatment of pain. The original NDA was submitted December 18, 2000, and received a Nonapproval Action on October 18, 2001. This is a resubmission (2nd cycle) dated July 27, 2006, due January 27, 2006.

ATTENDEES:

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization	Reviewer
Medical Team Leader:	Mwango Kashoki
Medical Officer:	Robert Levin
Statistical:	Barbara Elashoff/Dionne Price
Pharmacology:	Dan Mellon
Chemistry:	Sue Ching Lin
Biopharmaceutical:	Srikanth Nallani
DSI:	Carolanne Currier
Regulatory Project Management:	Lisa Basham

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☒ NO ☐
  If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? ☐ NO ☐
  YES

PHARMACOLOGY/TOX N/A ☐ FILE ☒ REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☒

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☒ NO ☐
- Sterile product? YES ☐ NO ☒
  If yes, was microbiology consulted for validation of sterilization?
  YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why: CLASS 2 RESPONSE

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☒ No filing issues have been identified.
- ☐ Filing issues to be communicated by Day 74. List (optional): N/A

ACTION ITEMS:

1. ☐ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. ☐ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. ☐ Convey document filing issues/no filing issues to applicant by Day 74.

Lisa Basham
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☒

*If "**No,**" skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES ☐ NO ☒

*If "**Yes,**" skip to question 7.*

4. Is this application for a recombinant or biologically-derived product?

YES ☐ NO ☒

*If "**Yes** "contact your ODE's Office of Regulatory Policy representative.*

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES ☐ NO ☒

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

*If "**No,**" to (a) skip to question 6. Otherwise, answer part (b and (c)).*

   (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

   (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes,**" (c), list the pharmaceutical equivalent(s) and proceed to question 6.*

*If "**No,**" to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.*
Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES ☒ NO ☐

(***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

*If "**No,**" to (a) skip to question 7. Otherwise, answer part (b and (c)).*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☒

(c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☒

*If "**Yes,**" to (c), proceed to question 7.*

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**No,**" to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s):
NDA 75-470 diclofenac potassium oral tablet 50 mg
NDA 21-005 diclofenac sodium topical gel 3%
NDA 20-037 diclifenac sodium solution/drops opthalmic 0.1%
NDA 19-201 diclofenac sodium tablet, delayed release, oral, 75 mg
NDA 74-376 diclofenac sodium tablet, delayed release, oral 25 mg, 50 mg

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES ☒ NO ☐

*If "**No,**" skip to question 8. Otherwise, answer part (b).*

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12. YES ☐ NO ☒

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

This application provides for a new dosage form and a new indication.

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☒

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☒

11. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO ☒

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES ☐ NO ☒

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☒ Not applicable (e.g., solely based on published literature. See question # 7

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

Patent number(s):

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug. N/A.

  YES ☐ NO ☐

  *If "**Yes**," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug*
  Was this listed drug product(s) referenced by the applicant? (see question # 2)

  YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

  N/A ☐ YES ☐ NO ☐

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES ☐ NO ☐

If "**Yes**," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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

/s/

Lisa Basham
1/26/2007 11:52:23 AM
CSO

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: 1/23/07

TO: Lisa Basham, Regulatory Project Manager
Robert Levin, MD, Medical Officer
Division of Anesthesia, Analgesia and Rheumatology Drug Products, HFD-170

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

FROM: Carolanne Currier, CSO
Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-234

APPLICANT: Institut Biochimique SA

DRUG: Diclofenac Epolamine Patch

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: Treatment of pain

CONSULTATION REQUEST DATE: 10/11/06

DIVISION ACTION GOAL DATE: 1/26/07

PDUFA DATE: 1/31/07

I. BACKGROUND:

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) which blocks the production of prostaglandins and has been shown to be effective at reducing pain and inflammation in the body. It has been approved for various pain indications and is marketed in tablet, solution, and gel forms. In December of 2000, Institute Biochemique SA (IBSA) submitted an NDA for a diclofenac patch (hydrophyllic transdermal system). The NDA (21-234) was not approved due to lack of reliability of the data. The Division of Anesthesia, Analgesia and Rheumatology Products (DAARP), found that the raw data did not always match the data submitted in clinical study summaries, and had concerns about sponsor oversight. IBSA resubmitted NDA 21-234 with new foreign clinical studies. DSI issued inspection assignments to verify the data from both French and German sites. The German site was selected because the study showed unusually positive results, and the French site was selected because it had the highest enrollment for protocol 050598.

The protocols for the two studies were as follows:

(French study) Protocol 050598: "A clinical study comparing the efficacy and safety of Flector Tissuegel® versus placebo in the treatment of minor ankle sprain." Protocol 050598 was a multicenter, randomized study in parallel groups, comparing the efficacy and safety of the diclofenac patch (Flector Tissuegel) vs. placebo. The study was to last for 7 days. Subjects were to be between 18 and 65 years of age and presenting with acute ankle pain resulting from a sprain that occurred within the last 24 hours. Initial subject pain evaluation was to have been $\geq$50 mm on a 100 mm visual analog scale (VAS). There was to have been no prior treatment for the pain. The primary efficacy endpoint was the change in the subjects' assessment of pain from the start to the end of treatment. Subjects were to be considered improved if there was a decrease in at least 20 mm on the VAS pain scale. Safety assessments were based on the subjects' spontaneous reporting of adverse events.

(UK/German study) Protocol 00GB/Fp05: "A randomised, double-blind, placebo-controlled study of the analgesic efficacy and safety of diclofenac epolamine patch in minor soft tissue injury." Protocol 00GB/Fp05 was a multicenter, double-blind, randomized assignment, placebo-controlled, parallel design trial of 2 weeks of continuous use of the Diclofenac Epolamine Patch. Subjects were to be between 18 and 85 years of age who had incurred a minor sprain, strain, or contusion within 72 hours of study entry. Initial pain severity was to be judged by the subject as at least 5 on a 0 – 10 category scale. The primary efficacy endpoint was the time to pain resolution. The pain was to be considered resolved if the pain fell 2 or more categories from initial assessment on the pain scale. Safety assessments were based on the subjects' spontaneous reporting of adverse events.

II. RESULTS (by protocol/site):

Name of Investigator	City, Country	Protocol	Inspection Date	Date EIR Received	Final Class.
Dr.	France	050598	1/15-19/07	Pending	Pending
Dr. med.	Germany	00GB/Fp05	1/15-19/07	Pending	Pending

Key to Classifications
NAI = No deviation from regulations.
VAI-No Response Requested= Deviations(s) from regulations.
VAI-Response Requested = Deviation(s) form regulations.
OAI = Significant deviations for regulations.

A. Protocol #050598

1. Dr. France, Site #12:

Observations noted below are based on verbal communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the establishment inspection report (EIR).

a. What was inspected: Dr enrolled 24 subjects into protocol 050598. Study records, including consent forms, medical histories, pain scales, global evaluations, drug accountability records, and sponsor correspondence were reviewed for all subjects during the inspection.

b. Limitations of inspection: None

c. General observations/commentary: The study appeared to have been conducted according to the protocol, however the following discrepancies in daily pain scores were noted between data reported on source documents and the data provided by the sponsor:

SUBJECT NUMBER	TREATMENT	DAY/HOUR	PAIN SCORE REPORTED ON SOURCE DOCUMENT	PAIN SCORE REPORTED ON DATA LISTING
10	Placebo	D0:H20	34	33
12	Flector	Baseline	74	72
126	Placebo	D7	36	31
165	Flector	Baseline	78	82
165	Flector	D0:H1	46	48
167	Placebo	D1:H20	55	50
167	Placebo	D2:H8	50	43

d. Data acceptability/reliability: DAARP should evaluate the significance and impact, if any, of the above pain score discrepancies on data acceptability.

B. Protocol #00GB/Fp05

1. Dr. med , Germany, Site #11:

Observations noted below are based on the communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

a. What was inspected: Dr. enrolled 44 subjects into protocol 00GB/Fp05. It is currently unknown how many subject records were reviewed during the inspection.

b. Limitations of inspection: None.

c. General observations/commentary: The study appeared to have been adequately conducted and no problems were noted with the data reported. There was nothing found to suggest inadequate sponsor oversight of the study.

d. Data acceptability/reliability: From the preliminary findings it appears the data from the Ottstadt site are acceptable and could be used to support an approval decision for the respective indication. There was no discernible reason for the unusually positive results noted by DAARP during the review of the data from this site. An addendum to this inspection summary will be generated if our conclusions change after receipt and review of the EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

DAARP should evaluate the significance and impact, if any, of the pain score discrepancies on the acceptability of the data from the — site. The data from the — site appear acceptable. There was no discernible reason for the unusually positive results from the Ottstadt site. There was no evidence of inadequate sponsor oversight at either site.

Observations noted above are based solely on preliminary verbal communications from the field investigators. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIRs.

{See appended electronic signature page}

Carolanne Currier, CSO

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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/s/

Carolanne Currier
1/23/2007 02:35:43 PM
CSO

Constance Lewin
1/23/2007 02:48:07 PM
MEDICAL OFFICER

1-18-07 DMETs request

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-234

DISCIPLINE REVIEW LETTER

Institut Biochimique SA (IBSA)
c/o: Clarence Jones, Ph.D., US Agent
8602 Mossford Drive
Huntington Beach, CA 92646

Dear Dr. Jones:

Please refer to your December 18, 2000 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Flector Patch (diclofenac epolamine topical patch) 1.3%.

The Division of Medication Errors and Technical Support, of the Office of Surveillance and Epidemiology, has reviewed your proposed labeling and has identified the following deficiencies and request for clarification.

1. PATCH LABEL:

   a. Ensure that each patch backing includes both the proprietary and established name of the drug. This information, as well as the product strength, should be prominent and readable on every patch backing.

2. POUCH LABEL:

   a. In order to ensure the safe disposal of the patch, include the following statement on the pouch label: "Fold used patches so that the adhesive side sticks to itself and safely discard used patches where children and pets cannot get to them."

   b. Decrease the size and relocate the company logo away from the proprietary and established names. The current presentation is distracting and interferes with the readability of the proprietary and established names. The proprietary and established name and product strength should have the greatest prominence.

   c. On the back of the pouch, ensure that the net quantity statement is located away from the product strength, preferably to the bottom third of the back panel.

d. On the back of the pouch, increase the prominence of the statement, "Change patch once every 12 hours. The treatment period should not exceed 2 weeks," and include these statements on the principle display panel.

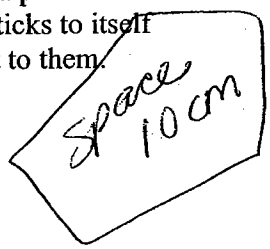
e. Increase the prominence of the statement, "IMPORTANT Reseal after opening."

f. We note a 3-month period of use after opening on the French product. Please comment on the applicability of this statement for the US product.

g. Add the statement, "Refer to full directions before using," underneath the directions for use pictorial.

h. In the directions for use, the fourth step indicates to "Remove patch if irritation occurs" but additional instructions on the steps the patients should take in the event of skin irritation and/or allergic reaction are omitted. Please refer patients to the package insert labeling for instructions on what to do should irritation and/or allergic reaction occur after the patch has been applied to the skin, e.g., add the statement, "See full prescribing information."

i. In the directions for use, include directions and a pictorial on how to discard used patches. For example, include the following statement along with a picture of a patch folded in half: "Fold used patches so that the adhesive side sticks to itself and safely discard used patches where children and pets cannot get to them."



3. CARTON LABELING

a. Change the word "expiry" to "exp" or "Expiration date."

b. The [redacted] font color on the [redacted] background is difficult to read. Revise the color to improve the readability of the strength.

c. See comments 2.a through 1.e

In addition, clarify whether you intend to [redacted]

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Lisa E. Basham, Regulatory Project Manager, at 301-796-1175.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Supervisory CSO
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
1/18/2007 04:11:22 PM

1-18-07 CMC Request

Basham, Lisa

From: Basham, Lisa
Sent: Thursday, January 18, 2007 9:33 AM
To: 'CLARENCE JONES'
Subject: 1-18-07 CMC request

Clarence, One more from the chemists....

To comply with ICH Q3A guidance, please revise the drug substance specification (refer to Attachment 1, Annex 9a of your 12/28/06 amendment) as follows:

1. Revise [redacted] to "Any individual unspecified drug-related impurity: NMT [redacted]

2. Add the following footnote for total impurities: "sum of all of reportable impurities above [redacted]

We will also ask the DMF holder to tighten the acceptance criterion for individual unspecified impurities as stated above.

Regards,

Lisa Basham, MS
Regulatory Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
301-796-1175
New email: lisa.basham@fda.hhs.gov

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

/s/

Lisa Basham
1/31/2007 02:00:41 PM
CSO

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; HFD-420)

DATE RECEIVED:	**DESIRED COMPLETION DATE:**	**OSE CONSULT #:**
October 3, 2006	December 22, 2006	2006-465
DATE OF DOCUMENT: July 27, 2006, September 12, 2006 and September 14, 2006	**PDUFA DATE:** January 31, 2007	

TO: Bob Rappaport, MD
Director, Division of Anesthesia, Analgesia and Rheumatology Products
HFD-170

THROUGH: Alina Mahmud, RPh, MS, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support

FROM: Tselaine Jones Smith, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support

PRODUCT NAME:	**NDA SPONSOR:** IBSA
Flector Diclofenac Epolamine) Transdermal System 1.3 % **NDA #:** 21-234	

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Flector. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in Section IV of this review to minimize potential errors with the use of this product. Additionally, please provide a sample of the backing to the patch for review and comment.

3. DDMAC finds the proprietary name, Flector, acceptable from a promotional perspective.

4. DMETS recommends that the Division contact the Office of New Drug Quality Assessment for guidance from the CDER Labeling and Nomenclature Committee, on clarification of the dosage form as outlined in Section IV of this review.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion if needed. If you have further questions or need clarifications, please contact Jenna Lyndly, Project Manager, at 301-796-2224.

Division of Medication Errors and Technical Support (DMETS)
Office of Surveillance and Epidemiology
HFD-420; WO 22; Mail Stop 4447
Center for Drug Evaluation and Research

PROPRIETARY NAME, LABEL AND LABELING REVIEW

DATE OF REVIEW: October 16, 2006

NDA #: 21-234

NAME OF DRUG: Flector (Diclofenac Epolamine) Transdermal System, 1.3%

NDA HOLDER: IBSA

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anesthesia, Analgesia and Rheumatology Products (HFD-170), for assessment of the proprietary name, Flector, regarding potential name confusion with other proprietary or established drug names. Container labels, carton and insert labeling were provided for review and comment from a medication error perspective.

PRODUCT INFORMATION

The Flector® Patch (diclofenac epolamine) is indicated for the relief of pain due to strains, sprains and contusions [redacted] It should be applied only to intact skin at the painful site. [redacted] . The Flector® Patch is comprised of an adhesive material containing 1.3% diclofenac epolamine which is applied to a non-woven polyester felt backing and covered with a polypropylene film release liner. The release liner is removed prior to application to the skin. Each adhesive base contains 180 mg diclofenac epolamine (13 mg per gram adhesive) in an aqueous base. The Flector® Patch is supplied in resealable envelopes, each containing 5 patches (10 cm x 14 cm) with one or two boxes per envelope.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3,4] for existing drug names which sound-alike or look-alike to Flector to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[5]. The SAEGIS™ Online service[6]

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[1] MICROMEDEX Integrated Index, 2006, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, Missouri.

[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-06, and the electronic online version of the FDA Orange Book.

[4] Phonetic and Orthographic Computer Analysis (POCA).

[5] www location http://www.uspto.gov/tmdb/index.html.

[6] Data provided by Thomson & Thomson's SAEGIS™ Online service, available at www.thomson-thomson.com

Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches.

In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies and one verbal prescription study, involving health care practitioners within the FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Flector. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC has no objections to the proposed proprietary name, Flector, from a promotional perspective.

2. The Expert Panel and independent review identified twenty-one proprietary names and two medical terms that were thought to have the potential for confusion with Flector. Of the twenty-three names identified, eight proprietary names (n=8) and one medical term (n= 1) warranted further evaluation based on look-alike, sound-alike and product characteristics (see Table 1 on page 4). Upon further review, it was determined that the remaining fourteen names lacked convincing look-alike and sound-alike similarities with Flector. In addition to there not being additional information on the drug name or the drug being taken off the market, the products also had numerous differentiating product characteristics such as product strength, indication for use, frequency of administration, prescription status, patient population and/or dosage formulation. Thus, the following names will not be discussed further in this review: Flutex, Fletcher's Castoria, Factor VIIa, Factor VIII, Factor IX, Flexicort, Flector (medical term), Crestor, Pletal, Fleet, Flexall, Plendil, Effexor and Flexeril.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Trecator	Ethionamide Tablets 250 mg	15 mg – 20 mg/kg/day; Initiate dose at 250 mg /day for 1-2 days, then increase to 250 mg twice daily for 1-2 days, with gradual increases to highest tolerated dose; average adult dose: 750 mg/day. Maximum dose: 1 gram/day in 3-4 divided doses	LA
Fludara	Fludarabine Powder for Injection 50 mg	25 mg/m^2 IV once daily for 5 days every 28 days. Three additional cycles should be given following the achievement of a maximal response.	LA
Fentora	Fentanyl Citrate Buccal Tablets 100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg	**Dose Titration** Patients should be titrated to a dose that provides adequate analgesia with tolerable side effects. **Starting Dose:** The initial dose should be 100 mcg.	LA
Floxin	Ofloxacin Solution: Otic, 0.3% (5 mL and 10 mL) Otic Singles™ 0.3% (0.25 mL) Tablets: 200 mg, 300 mg, 400 mg	**Tablet:** 200 mg - 400 mg twice daily dependent on indication **Solution:** Ten (10) drops (or the contents of two single dose containers) into affected ear(s) once or twice a day depending on the indication	LA/SA
Hectorol	Doxercalciferol Capsules: 0.5 mcg, 0.25 mcg Injection: 2 mcg/mL (2 mL)	Dose is individualized per patient and should be tolerated to lower iPTH to 150 pg/mL – 300 pg/mL, dose is adjusted at 8 week intervals ***Oral*** *Dialysis patients*: iPTH>400 pg/mL initial dose is 10 mcg 3 times per week at dialysis *Pre-dialysis patients*: initial dose is 1 mcg/day ***Intravenous*** *Dialysis patients:* iPTH>400 pg/mL Initial dose is 4 mcg 3 times per week after dialysis, administered as a bolus	LA/SA
Flextra	Acetaminophen/Caffeine/ Phenyltoloxamine Capsules 425 mg/35 mg/5 mg	One (1) capsule every 4 hours as needed for pain, congestion, fever relief for 10 days or less (or 3 days if used for fever) Do not take more than six (6) capsules in a 24-hour period.	LA/SA
Flextra DS	Acetaminophen/Phenyltoloxamine Tablets 500 mg/50 mg	One (1) tablet every 4 hours as needed for pain, congestion, fever relief for 10 days or less (or 3 days if used for fever)	LA/SA
Flextra 650	Acetaminophen/Phenyltoloxamine Tablets 600 mg/60 mg	One (1) tablet every 4 hours as needed for pain, congestion, fever relief for 10 days or less (or 3 days if used for fever)	LA/SA
Flexor (Medical Term)	N/A a muscle serving to bend a body part *Merriam-Webster's Medical Dictionary*, 2006, Merriam-Webster, Inc.	N/A	LA/SA

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Flector with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 125 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Flector (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

Outpatient RX: Flector # 1 patch apply 1 patch topically q 12. hrs.	Flector #1 Patch Apply 1 patch topically every 12 hours
Inpatient RX: Flector #1 patch topically q12 hrs	

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See appendix A for the complete listing of interpretations from the verbal and written studies.

C. SAFETY EVALUATOR RISK ASSESSMENT

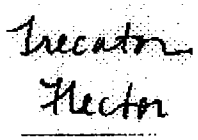
In reviewing the proprietary name Flector, the primary concerns relating to look-alike and sound-alike confusion with Flector are Trecator, Fludara, Fentora, Floxin, Hectorol, Flextra, Flextra DS, Flextra 650 and flexor. Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Flector.

Upon further analysis of the medical term flexor, DMETS will not review this name. "Flexor" is a medical term meaning "a muscle serving to bend a body part". Furthermore, because of the context in which the word "flexor" is likely to be used, it is unlikely that it would be confused with the name "Flector". In addition, the word "flexor muscle" is a noun that is usually used when one refers to "a muscle serving to bend a body part". Flexor is used as an adjective that is used to describe the muscles that bend body parts e.g. "flexor carpi ulnaris" and is not used within the context of prescription ordering. Therefore, DMETS feels that it is unlikely that the name Flector® Patch would be interpreted as meaning the medical term "flexor" in a written or verbal prescription order.

The remaining names of concern are discussed in detail below.

1. Trecator was identified as a name with similar appearance to Flector when scripted. Trecator (ethionamide) is indicated for the treatment of tuberculosis and other mycobacterial diseases, in conjunction with other antituberculosis agents, when first-line agents have failed or resistance has been demonstrated. Trecator is available as 250 mg tablets.

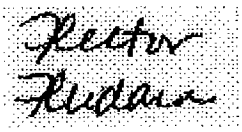
   Trecator and Flector may look similar as they are similar in length (8 letters vs. 7 letters) and they share identical middle letters "-ec-" and identical endings ("-tor"). In addition, the beginning letters "Tr" and "Fl" can look similar when scripted. However, the additional letter "a" in the name Trecator helps to distinguish between the two names when scripted.



   Trecator and Flector share an overlapping dosing frequency (twice daily). However, they differ in respect to dosage form (tablet vs. transdermal patch), route of administration (oral vs. topical), indication of use (tuberculosis vs. analgesic), and usual dose (250 mg to 750 mg per day vs. one patch). DMETS believes that the lack of convincing orthographic similarity and the differentiating product characteristics minimizes the potential for confusion between Trecator and Flector.

2. Fludara was identified as a name with similar appearance to Flector when scripted. Fludara (fludarabine) is indicated for the treatment of chronic lymphocytic leukemia. It is available as a 50 mg powder for injection.

   Flector and Fludara share identical beginning letters "Fl-" and may look similar as they contain the identical number of letters (seven). Furthermore, both names contain an upstroke in the middle position ("d" vs. "t") and the letters "ec" in Flector can look similar to the letter "u" in Fludara when scripted. However, the "-ara" at the end of Fludara and the "-or" at the end of Flector help to differentiate between the two names when scripted.



Fludara and Flector differ in indication for use (leukemia vs. analgesic), usual dose (25 mg/m^2 once daily for 5 days every 28 days vs. one patch), strength, frequency of administration (once daily for 5 days every 28 days vs. twice daily ., route of administration (intravenous vs. topical) and dosage form (injection vs. transdermal patch). DMETS believes that these product differences will minimize the risk of confusion and error between Fludara and Flector.

3. Fentora was identified as a name with similar appearance to Flector when scripted. Fentora (fentanyl citrate) was recently approved (September 25, 2006) for the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.

Fentora and Flector share the letters "tor" in similar positions. However, the upstroke of the letter "l" in Flector along with the letter "a" at the end of the name Fentora help to differentiate the two names when scripted.

Fentora and Flector share the same indication of use (analgesia); however, the patient populations for the type of pain control differ (cancer vs. . The two products have several differentiating product characteristics such as strength, dosing frequency (varies per patient vs. twice daily), dosage form (buccal tablet vs. transdermal patch) and route of administration (oral vs. topical). Additionally, Fentora is classified as a Schedule II controlled substance which requires more stringent prescribing and dispensing practices. Furthermore, since Fentora is a buccal tablet, a prescription is likely to include instructions indicating that the buccal tablet should be applied to the inside of the jaw.

DMETS believes that the lack of convincing orthographic similarity and the differentiating product characteristics minimize the potential for confusion between Fentora and Flector.

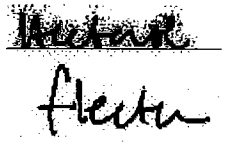
4. Floxin has been identified as a name with similar sound and appearance to Flector when spoken. Floxin (ofloxacin) is indicated for the treatment of infections such as bronchitis, gonorrhea, ear, skin, urethitis and cervicitis, pelvic inflammatory disease, cystitis, urinary tract, and prostatitis. Floxin is available as a 0.3% otic solution and as 200 mg, 300 mg and 400 mg tablets.

Phonetically, Floxin and Flector share two syllables and the same beginning "Fl" sound in the first syllable. However, the second syllables ("-xin" vs. "-tor") sound different thereby differentiating the two names when spoken. Orthographically, Floxin and Flector have identical beginnings "Fl" and the "x" in Floxin can look similar to the "t" in Flector. However, the remaining letters help to differentiate the names.

Floxin and Flector can share an overlapping frequency of administration (twice daily). However, they differ in route of administration (oral vs. topical), usual dose (200 mg to 400 mg twice daily vs. one patch), strength, dosage form (otic solution and tablets vs. transdermal patch) and indication of use (infection vs. analgesia). Although both the Floxin otic solution and the Flector Patch may be prescribed "as directed", orders for Floxin otic solution will likely include the affected ear (left ear, right ear, and both ears), indicate the number of drops to use and/or the dosing frequency which will help to lessen the confusion between the name pair. Thus, DMETS considers the likelihood of medication errors resulting from confusion between these products to be low.

5. Hectorol was identified as a name with similar sound and appearance to Flector. Hectorol (doxercalciferol) is indicated for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease. It is available as 0.5 mcg and 0.25 mcg capsules and as a 2 mcg/mL (2 mL) injection.

   Hectorol and Flector share the "tor" sound when spoken. However, the "H" and the "F" sounds at the beginnings of each name along with the three syllables in the name Hectorol help to differentiate the two names when spoken. Orthographically, both names share the letters "ect" in similar positions. Additionally, the letters "Fl" and "H" can look similar when scripted. However, the ending letters ("-ol") of Hectorol helps to distinguish between the two names when scripted.



   Hectorol and Flector differ in frequency of administration (3 times per week vs. twice daily), route of administration (oral and intravenous vs. topical), usual dose (individualized per patient vs. one patch every 12 hours), strength, dosage form (capsule and injection vs. transdermal patch), duration of use (3 times per week vs. [redacted], and indication of use (secondary hyperparathyroidism vs. analgesia). DMETS believes that these product differences will minimize the risk of confusion and error between Hectorol and Flector.

6. Flextra, Flextra DS and Flextra 650 have been identified as names with similar sound and appearance to Flector. This product line is indicated for treatment of the aches and pains of colds or flu, menstrual cramps, headache, or fever. They may also be used to relieve pain in certain kinds of arthritic conditions. Flextra contains the combination of acetaminophen, caffeine and phenyltoloxamine (425 mg/35 mg/ 45 mg); Flextra DS contains the combination of acetaminophen and phenyltoloxamine (500 mg/50 mg); and Flextra 650 contains different strengths of the combination of acetaminophen and phenyltoloxamine (600 mg/60 mg).

   Phonetically, the first syllable of both Flextra and Flector sound identical ("Flex-" and "Flec-"). However, the "-tra" sound at the end of Flextra is different from the "-tor" sound at the Flector thereby distinguishing between the two names when spoken.

Orthographically, Flextra and Flector share the same beginning letters ("Fle-") and the letter "t" in the same position. In addition, the letter "x" in Flextra can look similar to the letter "c" in Flector when scripted. Moreover, the endings of the two names ("-tra" vs. "-tor") can look similar if they are written in such a manner that the ends trail off when scripted. However, Flextra DS and Flextra 650 can be differentiated in script if Flextra is written with the modifiers DS and 650.

Flextra and Flector share an overlapping indication of use (analgesia). However, they differ in frequency of administration (every four hours vs. twice daily), route of administration (oral vs. topical), usual dose (one capsule/tablet vs. one patch), strength and dosage form (tablet and capsule vs. transdermal patch).Since Flextra has a maximum daily dose, prescribers are more likely to write out the dose and frequency which differs from prescriptions for Flector. Based on the product characteristics listed above, DMETS believes that the likelihood for confusion is minimal between Flextra and Flector.

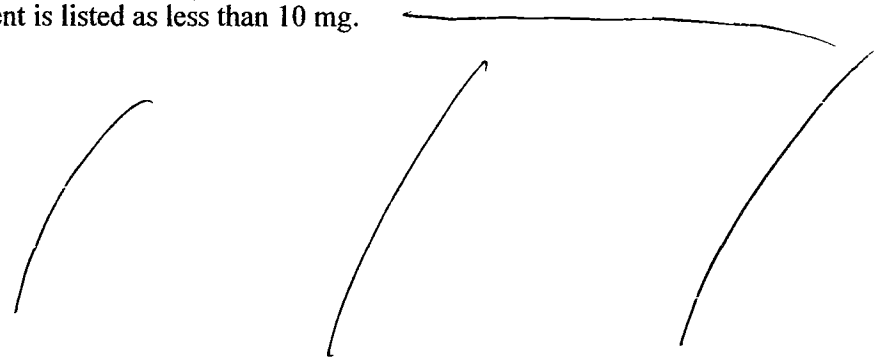
IV. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the container labels, carton and insert labeling of Flector, DMETS has focused on safety issues relating to medication errors. DMETS has identified the following areas of improvement, which might minimize potential user error.

A. GENERAL COMMENTS

1. We note that this transdermal patch is applied twice daily. This application time is not consistent with other prescription transdermal products as most transdermal products are applied for a twenty-four hour period and removed. The twice daily application frequency of Flector differs from the normal once daily application which may lead to confusion among patients and caregivers. Therefore, in order to minimize application problems, DMETS recommends placing the dosing interval on the principal display panel of the pouch label and carton labeling.

2. The amount of drug released from the transdermal system per 12 hours is not clearly cited in the labels and labeling. The strength is currently presented on the container label and labeling as a percent. Additionally, in the insert labeling, the amount of drug received by the patient is listed as less than 10 mg.



3. There is a discrepancy in the labels and labeling with regards to the total amount of drug each patch contains. The pouch label and carton labeling list the total drug content of each patch as 180 mg diclofenac epolamine, while the package insert labeling list the total drug content of each patch as — .ng diclofenac epolamine. Please revise so that the total drug content is consistent.

4. The dosage form 'Patch" is not a recognized U.S. Pharmacopeia dosage form. DMETS recommends consulting the Office of New Drug Quality Assessment, specifically the CDER Labeling and Nomenclature Committee (LNC), on the proper designation of the dosage form. Once this has been resolved all labels and labeling should include the dosage form with the established name.

5. DMETS is concerned that some patients will use multiple Flector patches concurrently. From a medication safety perspective, DMETS is concerned with these practices since the safety and efficacy of the Flector Patch has not been studied under these conditions. Post-marketing experience with other transdermal delivery systems has shown that the use of multiple patches concurrently (intentional and unintentional) to be associated with adverse outcomes related to overdosage of the drug. Therefore, DMETS recommends that the sponsor update the insert labeling to include warnings on the effects of using multiple patches.

6. DMETS is concerned that the concomitant administration of other prescription and over-the-counter oral and/or topical analgesic products (e.g. NSAIDS, aspirin, acetaminophen, narcotics, Voltaren (oral diclofenac) and Solaraze (topical diclofenac)) with the Flector Patch could lead to medication errors and overdose. Additionally, in a hospital setting, research has shown that prescribing the same or similar medication to be given concurrently by two different routes of administration to be a common source of medication error.[7] The same study indicated the prescribing of the same or similar medication to be given concurrently via the transdermal and oral route of administration as the second most common type of prescribing error. Although DMETS believes that this risk is decreased by the use of different proprietary names, we feel that there will be confusion by both patients and practitioners to more readily identify the commonality of the medications, even when given by different routes, thus, leading to a medication error. Therefore, DMETS recommends that the sponsor educate both healthcare providers and patients about the potential for harm associated with using the Flector Patch in conjunction with other analgesic agents.

7. DMETS recommends that each patch be packaged individually in order to help prevent the application of all patches contained in the pouch at once and decrease the possibility that the effectiveness of the product may be affected if the pouches are accidentally left open once the patch is removed.

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[7] Lesar TS. *Medication Prescribing Errors Involving Route of Administration*. Hosp Pharmacy. 2006; 41(11): 1053-1066.

B. PATCH LABEL

1. DMETS notes that the patch backing was not provided for review and comment. Please provide the patch backing. In addition, ensure that each patch backing includes both the proprietary and established name of the drug. This information, as well as the product strength, should be prominent and readable on every patch backing.

2. DMETS notes that the sponsor did not provide the color of the patch. We recommend

3. In order to ensure the safe disposal of the patch, DMETS recommends including the following statement on the patch backing: **"Fold used patches so that the adhesive side sticks to itself and safely discard used patches where children and pets cannot get to them."**

C. POUCH LABEL

1. See Comment B3.

2. DMETS recommends decreasing the size and relocating the sponsor's logo away from the proprietary and established names. The current presentation is distracting and interferes with the readability of the proprietary and established names. The proprietary and established name and product strength should have the greatest prominence.

3. Increase the prominence of the "Rx Only" statement and relocate to the bottom one-third of the primary display panel.

4. Revise to include the route of administration on the principal display panel.

5. Revise so that the statement of product strength immediately follows the established name.

6. Relocate the net quantity statement away from the product strength, preferably to the bottom third of the back panel.

7. Bold and highlight the statement "Change patch once every 12 hours. Include these statements on the principal display panel.

[8] Institute for Safe Medication Practices Press Release: ISMP calls for more action to safeguard pain patches. August 13, 2005.

8.

9. Add the statement "Refer to full directions before using" underneath the directions for use pictorial.

10. DIRECTIONS FOR USE

a. The fourth step indicates to "Remove patch if irritation occurs" but additional instructions on the steps the patients should take in the event of skin irritation and/or allergic reaction are omitted. Please refer patients to the package insert labeling for instructions on what to do should irritation and/or an allergic reaction occur after the patch has been applied to the skin.

b. Revise to include directions (and a pictorial) on how to discard used patches. For example include the following statement along with a picture of a patch folded in half: **"Fold used patches so that the adhesive side sticks to itself and safely discard used patches where children and pets cannot get to them."**

D. CARTON LABELING

1. See Comments B3 and C1 through C10.

2. Change the word 'expiry' to 'exp' or 'expiration date'.

3. The font color on the background is difficult to read. Revise the color to improve the readability of the strength.

E. INSERT LABELING

1. DMETS was not provided evidence regarding exposure of the Flector Patch to heat or hot conditions. Post-marketing surveillance with other transdermal delivery systems has identified cases in which inadvertent exposure to heat sources (e.g. using heating pads with fentanyl transdermal systems; sun exposure with Ortho Evra) resulted in adverse events. DMETS recommends that the sponsor update the insert labeling to include warnings of exposure to heat or hot conditions if warranted.

2. DMETS was not provided evidence regarding the use of overlays with the Flector Patch. Post-marketing surveillance regarding the use of overlays with the fentanyl transdermal system was found to increase the rate and extent of absorption, which resulted in patient harm and death in some cases. The use of bandages, band aids and other overlays to secure the patch may unintentionally produce an increase in temperature at the site of absorption. DMETS is concerned that the use of such measures over part of or the entire system could likewise affect the absorption of diclofenac from the Flector Patch, thereby putting patients at risk if the drug is delivered too quickly or an excessive dose is delivered. Therefore, DMETS recommends that the sponsor update the insert labeling to include warnings on the use of overlays with the Flector Patch.

3. DMETS was not provided evidence regarding exposure of the Flector Patch to cold. Many healthcare practitioners recommend that patients apply cold compresses or ice to the strains, sprains and contusions associated with sports injury. DMETS is concerned that patients will apply cold compresses to the injured area in addition to the Flector Patch. In addition, DMETS questions how exposure cold conditions will affect the integrity of the transdermal system. Thus, DMETS recommends that the sponsor update the insert labeling to include warnings on the use of cold compresses or ice on the Flector Patch.

4. DMETS was not provided evidence regarding the adhesion of the Flector Patch after exposure to sweat, bathing, swimming or showering. Based on post-marketing experience with other transdermal delivery systems, DMETS believes that exposing the patch to water or sweat may affect the adhesiveness of the patch thereby causing it to curl up on the edges, wrinkle or fall off. Hence, DMETS recommends that the sponsor update the insert labeling to include information and instructions on what to do in the event that a patch curls up on the edges, wrinkles or falls off.

5. DMETS was not provided evidence of the integrity of the Flector Patch in the event that the patch is cut. Based on post-marketing experience with other transdermal delivery systems (e.g. Daytrana), DMETS believes that cutting the patch could violate its integrity. Additionally, this transdermal system is very large and depending upon where the patient is applying the patch, they may cut the patch to fit at the application site. The release of the drug may be affected which could pose a health risk to the patients wearing the cut patches. Therefore, DMETS recommends that the sponsor update the insert labeling to include warnings on the effects of cutting the patch.

6. DMETS questions whether or not there will be irritation at the site of pain if a transdermal system is repeatedly placed in the same location on the skin for a period of two weeks. Can subsequent transdermal systems be located to a different area near the site of pain or should patients discontinue use? Therefore, DMETS recommends that the sponsor update the insert labeling to include instructions on whether or not that transdermal system can be rotated to different locations at the site of pain.

7. Revise the insert labeling to include instructions on how to remove the patch and adhesive if they become difficult to remove from the patient's skin.

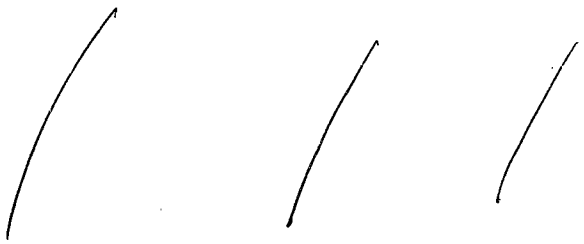
8. WARNINGS

   In the section entitled *'Excessive Dosing'*, the package insert labeling states that "When combined with oral diclofenac and other NSAID therapy, the entire systemic burden should be taken into account". Due to DMETS concern that oral nonsteroidal anti-inflammatory agents (NSAIDS) will be used in combination with the Flector Patch, this section should include the type(s) of systemic burden the patient will experience if the product is taken with other NSAIDS.

9. PRECAUTIONS

   a. See General Comment A3.

b.



10. DOSAGE AND ADMINISTRATION

11. HANDLING AND DISPOSAL

a. See Comment B3.

b. Revise [redacted] to read as "Patients and caregivers should wash their hands after applying, handling or removing the patch. Eye contact should be avoided."

Appendix A: Prescription Study Results for Flector

Inpatient	Outpatient	Voice
Flector	Flector	Flector
Flector	Flector	Flector
Flector	Flector	Flecktor
Zlector	Flector	Flector
Flector	Flector	Flector
Flector	Flector	Flextor
Flector	Flector	Flector
Flector	Flector	Flector
Flector	Flector	
Hector	Flector	
Flector	Flector	
Flector	Flector	
Flector		
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Flector		

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/s/

Tselaine Jones-Smith
1/12/2007 11:58:56 AM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
1/12/2007 12:00:49 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
1/12/2007 02:01:37 PM
DRUG SAFETY OFFICE REVIEWER
Also signing for Carol Holquist, DMETS Director, in her absence

A

4 Page(s) Withheld

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_____ Draft Labeling

_____ Deliberative Process

1-11-07 Pharm/Tox Request

Basham, Lisa

From: Basham, Lisa
Sent: Thursday, January 11, 2007 12:03 PM
To: 'CLARENCE JONES'
Subject: 1-11-07 Pharm/Tox request

Clarence, Below are some requests from the P/T reviewer. As the PDUFA date is coming rapidly, please respond ASAP.

1) The composition of the Flector Plaster that was studied in the 28-day repeat dose dermal irritation studies was not included in the study reports 920629 and 920629A. Please provide a table listing the quantitative composition of active and inactive ingredients of the Flector Plaster evaluated in those studies and how that formulation compares to the proposed drug product.

2) Your proposed drug product label

3) Your proposed drug product label

4) Your proposed drug product label

Warm Regards,

Lisa Basham, MS
Regulatory Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
301-796-1175
New email: lisa.basham@fda.hhs.gov

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/s/

Lisa Basham
1/12/2007 10:38:31 AM
CSO

1-8-07 CMC Request

Basham, Lisa

From: Basham, Lisa
Sent: Monday, January 08, 2007 3:23 PM
To: 'CLARENCE JONES'
Subject: 1-8-07 CMC Info Req

Attachments: 1-8-07 CMC Info Req.doc

Hi, Clarence,

One more from the Chemists....

1-8-07 CMC Info Req.doc (57 KB...

Lisa Basham, MS
Regulatory Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
301-796-1175
New email: lisa.basham@fda.hhs.gov

NDA 21-234, Diclofenac Epolamine Topical Patch
CMC Information Request #3 for the Resubmission

1. The in-process control, which wa[redacted] is inadequate. (Refer to Response #6 in the 7/27/06 submission)

2. Revise the drug release acceptance criteria (refer to Annex 9b of the 12/28/06 amendment). Based on the provided data, the following acceptance criteria are recommended:

   Percentage of the labeled amount of diclofenac epolamine released at the following time points:

   30 minutes: ≥
   60 minutes: ≥
   120 minutes:

3. The following comments pertain to the labeling of the drug product:

   (a) Title and Description sections of the package insert:

   Revise the complete chemical name to the following:

   2-[(2,6-dichlorophenyl)amino]benzeneacetic acid, 2-(pyrrolidin-1yl)ethanol salt

   (b) "How supplied" section of the package insert:

   Include embossed information.

   (c) Envelope and carton labeling

   (i) To make it clear, add the subheading "Inactive Ingredients:" in front of the list of inactive ingredients.

   (ii)

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/s/

Lisa Basham
1/12/2007 10:04:53 AM
CSO

Basham, Lisa

From: Basham, Lisa
Sent: Wednesday, December 20, 2006 12:03 PM
To: 'CLARENCE JONES'
Subject: Clarification re: annotated label request

Clarence,

I think we need to clarify what we mean by an annotated label, based upon your response below. In the original NDA submission, the only references for certain information provided in the clinical pharmacology, chemistry, and non-clinical sections were to studies conducted by the sponsor. For example:

From the response below, it appears that the same thing will be done for this latest label. That limited amount of referencing is not sufficient for our purposes. We need to know the source of all information they put in the label. For example, under "drug interactions," the sponsor should list the source of information regarding the interaction between diclofenac and aspirin (i.e. they should cite the article, product label, textbook, or whatever was the source for this information.)

Lisa Basham, MS

Regulatory Project Manager

1/9/2007

Division of Anesthesia, Analgesia and Rheumatology Products

301-796-1175

New email: lisa.basham@fda.hhs.gov

Lisa Basham, MS
Regulatory Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
301-796-1175
New email: lisa.basham@fda.hhs.gov

From: CLARENCE JONES [mailto:cejtwsxx@verizon.net]
Sent: Tuesday, December 19, 2006 4:50 PM
To: Basham, Lisa
Cc: Malandro, Lisa
Subject: Re: NDA 21-234 Diclofenac

Dear Lisa,

Status report (in red) on the items you requested late last week and this week to date:

<<21234_resubmission_IR#2.doc>>

I am waiting for one item from the Japanese manufacturer of the finished product. Anticipate sending no later than Thursday of this week but perhaps tomorrow.

For US-01 (Sports 01) provide a table summarizing the disposition status of all randomized patients by treatment group.
The table should indicate the number of patients who completed 14 days of treatment and the specific reasons for discontinuation of all other patients. Indicate the source data set for this table.

In section 5.2 Patient Disposition - Integrated Summary of Safety and Effectiveness (included in Amendment 13), Table 3 is referenced which includes the disposition data for US-01 as excerpted from section 10.1 of the final US-01 report. Since we (my statistician and I) are not as familiar with database for US-01 as we are for the UK/German study, it has taken some time to find the source material for this information. However, by tomorrow morning I anticipate we will be able to fulfill this request. Please note that the disposition data as presented in Table 3 are not expected to change, but a SAS file containing the source data for the table will be provided for convenience.

Can you please submit an annotated label?
The annotated version should indicate all of the sources for the information described in the PI. Details regarding the sources for the non-clinical and clinical pharmacology information are especially important.

The sponsor has assigned three people to annotate the product insert that has been modified to accommodate the recommendations in 21234_resubmission_IR#2.doc. Please note that annotation will reference information in the original submission as well as one or more of the subsequent amendments. I am hopeful that this process can be completed by tomorrow morning as well.

I will forward information to you via e-mail as soon as it becomes available, but will wait to send as an official amendment until all requests have been filled.

Regards,

CJ

P.S. Hope you are feeling better.

Basham, Lisa

From: Malandro, Lisa
Sent: Tuesday, December 19, 2006 10:28 AM
To: 'cejtwsxx@verizon.net'
Cc: Basham, Lisa
Subject: NDA 21-234 Diclofenac

Clarence,
Can you please submit an annotated label?
The annotated version should indicate all of the sources for the information described in the PI. Details regarding the sources for the non-clinical and clinical pharmacology information are especially important.
Thanks,
Lisa

Lisa Malandro
Regulatory Health Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products; HFD-170
301-796-1251
fax-301-796-9722

Basham, Lisa

From: Basham, Lisa
Sent: Monday, December 18, 2006 10:48 AM
To: 'CLARENCE JONES'
Subject: 12-18-06 Clinical Request

Clarence,

We need the following information as soon as possible (by close of business tomorrow if possible):

For US-01 (Sports 01) provide a table summarizing the disposition status of all randomized patients by treatment group. The table should indicate the number of patients who completed 14 days of treatment and the specific reasons for discontinuation of all other patients. Indicate the source data set for this table.

Thanks!

PS. Please confirm receipt.

Lisa Basham, MS
Regulatory Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
301-796-1175
New email: lisa.basham@fda.hhs.gov

12-14-06 CMC Request

Basham, Lisa

From: Basham, Lisa
Sent: Thursday, December 14, 2006 9:37 AM
To: 'CLARENCE JONES'
Subject: CMC request

Attachments: 21234_resubmission_IR#2.doc

As I said.....

21234_resubmissio
n_IR#2.doc (6...

Lisa Basham, MS
Regulatory Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
301-796-1175
New email: lisa.basham@fda.hhs.gov

NDA 21-234, Diclofenac Epolamine Topical Patch
CMC Information Request #2 for the Resubmission

1. The following comments pertain to the drug substance specification:

   (a) Your submission dated 7/26/06 included a response to the FDA CMC comment 2b with a statement that the drug substance specification was revised to replace Ph. Eur. methods with USP methods as appropriate. However, the drug substance specification that was provided in Annex 9a of the 9/14/06 amendment does not reflect this revision. Please reconcile this discrepancy.

   (b) Provide the full chemical name for the impurity in the drug substance specification table (or in the footnote of the table), indicating that it is

2. The drug product specification, as provided in Annex 9b of the 9/14/06 amendment, does not include the second identification test (as revised in the 7/26/06 submission). There is a typo (NLT or NMT?) in the acceptance criterion for Provide a revised version of the drug product specification including the following:

   (a) Updated acceptance criteria for the "description" test with information describing the embossed patch

   (b) A second identification test as described in the 7/26/06 submission)

   (c) Updated acceptance criteria for degradants including:
   - any unspecified drug-related degradation product with a threshold no more than the identification threshold,
   - total degradation products (sum of all reportable degradation products above
   - the correct limit for mpurity. Provide the chemical name of impurity.

   (d) At least two additional time points in the acceptance criteria for drug release (e.g. 30, 60, and 120 minutes)

3. Revise the stability protocol to reflect the revised drug product specifications recommended above.

4. The following comments pertain to the labeling of the drug product:

   (a

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/s/

Lisa Basham
1/12/2007 10:04:20 AM
CSO

Basham, Lisa

From: Basham, Lisa
Sent: Tuesday, December 12, 2006 1:05 PM
To: 'CLARENCE JONES'
Subject: Clarification and one additional question.

Clarence,

Here you go...

1. The CRF should have been for patient 73 in the French Study (Protocol 05-05-98).

2. Also need clarification regarding the following statement contained in the UK/German Study, Section 15.1 (Primary Outcome Variable): "Interday pain score comparisons reached significance by the time the second patch was removed on day 1..." Explain what "day 1" means in the above statement given that the second patch is removed approximately 24 hours after application of the first patch which would be the second day of the study.

Thanks!

Lisa Basham, MS
Regulatory Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
301-796-1175
New email: lisa.basham@fda.hhs.gov

Basham, Lisa

From: Basham, Lisa
Sent: Thursday, December 07, 2006 11:04 AM
To: 'CLARENCE JONES'
Subject: FW: N 21-234 (diclofenac patch) - Information Request

Lisa Basham, MS
Regulatory Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
301-796-1175
New email: lisa.basham@fda.hhs.gov

From: Kashoki, Mwango
Sent: Wednesday, December 06, 2006 11:19 AM
To: Basham, Lisa; Levin, Robert A
Subject: N 21-234 (diclofenac patch) - Information Request

Clarence, One more.....

For protocol 00G/Fp05 (the UK/German study), indicate where in the NDA the protocol allows for reclassification of disposition status (i.e. completion or discontinuation of the study), as well as describes the methods/rationale for reclassification. Clarify whether reclassification occurred before or after unblinding of patients' treatment assignment.

12-7-06 thru 1-307
Clinical Requests

Basham, Lisa

From: Basham, Lisa
Sent: Thursday, December 07, 2006 11:03 AM
To: 'CLARENCE JONES'
Subject: FW: N 21-234 - Diclofenac epolamine patch - Information request

Clarence, Please see the clinical request below. Please tell IBSA that we need this response ASAP. Thanks!!

Lisa Basham, MS
Regulatory Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
301-796-1175
New email: lisa.basham@fda.hhs.gov

1.
The information regarding the disposition of patients in Study 05-05-98 is inconsistent. In Amendment 14, the Study Enrollment/Completion table indicates that 134 patients enrolled in, and 126 patients completed the study – implying that 8 patients dropped out. However the study report shows only 7 patients who dropped out of the study (Section 10.1, "Subjects Dropped out from the Study"). Furthermore, dataset db050598.xpt lists patients 41, 42, 43, and 158 as having dropped out of the study (variable DROP_J7), yet data regarding patch use (variables QUOT_J3 and MAN_A_J7) suggest that these patients used a patch over the entire duration of the trial. Also, these patients are not included in the list "Subjects Dropped out from the Study.".,

a) Provide a table listing the disposition status of patients in both the active and placebo groups. Indicate how many patients in each group were enrolled, randomized, completed, or dropped out. The specific reason for dropout (adverse event, loss to follow up, lack of efficacy (e.g. including initiation of other analgesic therapy) etc.) should be provided.
b) Explain the discrepancy in the data regarding the disposition status and drug use for patients 41, 42, 43 and 158 and provide the correct disposition status for these four patients.
c) Provide the CRFs for patients 41, 42, 43 and 158.

2.
Protocol 05-05-98 excluded patients who had their ankle sprain treated prior to study entry. Clarify whether use of ankle braces or crutches was allowed, and what questions during the screening and the double-blind phases would identify patients who used a brace or other assistive device to assist with ambulation?

3.
Protocol 05-05-98 specified that an examination of the skin at the application site would be performed at D0, D3, and D7. Indicate where on the CRF data regarding skin condition at D3 and D7 was captured, and identify the corresponding variables in the db050598.xpt dataset.

4.
Protocol 05-05-98 excluded patients treated by enzyme therapy either locally or by oral route. Clarify what comprises "enzyme therapy."

5.
Submit Form 3454, "Certification: Financial Interests and Arrangements of Clinical Investigators" for Study 05-05-98 .

6.

Section 14.4 of the study report for the UK/German Study (00GB/Fp05) describes discrepancies between the disposition data captured on the Exit Visit form (and in the exit.xpt dataset) and the reclassified reasons for discontinuation as shown in Table 3 of the report (and in the exit2.xpt dataset). The basis for reclassification is unclear. Therefore, based on information on the Exit Form of the CRF, reclassify patients' disposition status as follows:

- Patients who "discontinued in favor of another therapy" or use of a prohibited analgesic medication should be classified as discontinuing due to lack of efficacy.
- Patients discontinuing due to *any* adverse event (including SAE or death) should be classified as discontinuing to due an adverse event.
- Patients who "wished to withdraw for any other reason [than an AE, other therapy or injury resolution]" should be classified as discontinuing due to "other" reasons.
- Patients who were removed from the trial before completing 14 days of treatment because they were non-compliant with study procedures (e.g. diary entry) or did not meet eligibility criteria should be classified as discontinuing due to protocol violations.
- Patients who withdrew consent for *non treatment-related* reasons should be classified as discontinued due to withdrawal of consent. Patients who cite continued pain or adverse events as reasons for consent withdrawal should be reclassified appropriately.

Subjects who completed 14 days of treatment should not be considered to have withdrawn from the study. Both of the variables RTNPCHNO and PTRTDAY of the exit.xpt dataset should be used to confirm study completion. If there is a discrepancy between the two, a reason for selection of one or the other should be provided.

Based on the new classification, complete the following table:

	Diclofenac Epolamine Patch, N =	Placebo, N =
No. Patients	N (%)	N (%)
Enrolled		
Randomized		
Completed 14 days of therapy		
Discontinued		
Injury resolution		
Lack of efficacy		
Adverse event		
Loss to follow-up		
Protocol violation		
Withdrew consent		

Provide the dataset used to derive the above table.

7.
Submit the CRF for patient 73 in the UK/German study (00GB/Fp05).

Let me know when you can pull this info together.

Lisa Basham, MS
Regulatory Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
301-796-1175
New email: lisa.basham@fda.hhs.gov

10-25-06
Clinical Req.

Basham, Lisa

From: Basham, Lisa
Sent: Wednesday, October 25, 2006 1:19 PM
To: 'cejtwsxx@verizon.net'
Subject: Clinical Request fro NDA 21-234

Hi Clarence!

Please see the requests below from the clinical reviewer regarding NDA 21-234.

1.
The primary efficacy variable in Protocol 05-05-98 was pain on active mobilization. Provide a description of the procedure used for evaluating pain on active mobilization.

2
Protocol 05-05-98 described use of a strap and required record of this use in the CRF. Clarify what a "strap" is and how it differs from protective wraps and elastic compression bandages used to secure the patch in place. Provide a list of the patients that used a strap.

3.
In the integrated summary of safety and effectiveness, no serious adverse events (SAEs) are reported. However, three patients are listed in the ISS dataset as having serious adverse events: PTID 10536, 20122 and 40440. Clarify the discrepancy, and provide CRFs and narratives for those three patients and any other patient with a SAE.

4.
For the two US trials, list the patients who discontinued due to an adverse event, and the event that led to dropout. Also, provide the corresponding narratives for these patients.

Thanks, Clarence!

Let me know when you can pull this info together.

Lisa Basham, MS
Regulatory Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
301-796-1175
New email: lisa.basham@fda.hhs.gov

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/s/

Lisa Basham-Cruz
10/25/2006 03:16:17 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006.

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	
See Appendix A	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME		TITLE	
Giuseppe Mautone	Clarence Jones	IBSA Director R&D	Consultant to IBSA
FIRM / ORGANIZATION			
Institut Biochimique SA (IBSA)			
SIGNATURE		DATE	
		9/5/2006 9-26-06	

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (2/03)

C

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_____ Deliberative Process

8-11-06 Admin. Request

Basham, Lisa

From: CLARENCE JONES [cejtwsxx@verizon.net]
Sent: Monday, September 04, 2006 6:21 PM
To: Basham, Lisa
Subject: Fw: NDA 21-234; Jason Hartman Request for Additional Information

Dear Lisa,

I have everything requested below except I am not certain what is meant by a color mock-up of the container. The patches are supplied five per resealable envelope, with one or two envelopes placed in a carton. Is the container the envelope?

Do you want me to simply attach each of the items requested below to an e-mail directed to you. Or should I copy each item onto a CD and send it as correspondence to the same location as Amendment 13 below, along with a cover letter explaining the reason for the submission?

Bob Rappaport, M.D.
Division Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Thanks!

CJ

Clarence Jones, Ph.D.

Consultant to IBSA

8602 Mossford Drive

Huntington Beach, CA 92646

(714) 963-0078 (phone/fax)

cejtwsxx@verizon.net

----- Forwarded Message ----

From: "Hartman, Jason" <Jason.Hartman@fda.hhs.gov>
To: cejtwsxx@verizon.net
Sent: Friday, August 11, 2006 8:37:56 AM
Subject: NDA 21-234

Dear Dr. Jones:

My name is Jason Hartman and I am the Project Manager responsible for NDA 21-234 (Diclofenac Epolamine Patch). You should be receiving (if you haven't already) a letter dated August 9, 2006 acknowledging receipt of your July 27, 2006 re-submission.

I have performed a preliminary review of your re-submission and request that you submit the following forms/information to the NDA as a Correspondence:

1. Financial Disclosure – Update the information submitted with the original application and include Form 3454 and/or Form 3455, which need to be signed by you and IBSA. Here are the links to the forms:

Form 3454 http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3454.doc

Form 3455 http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3455.doc.

2. Debarment Certification – To be signed by you and IBSA. **NOTE:** Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."

3. Patent Certification – Update the information submitted with the original application, if applicable, and include Form 3542a. Here is the link to the form: http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3542a.doc.

4. Form 356h – To be signed by you and IBSA. In addition, in the "IF AN NDA, IDENTIFY THE APPROPRIATE TYPE" section, please check the 505 (b)(2) box rather than the 505 (b)(1) box.

In addition, please provide a color mock-up of the carton and container. This may be submitted as a labeling amendment.

And finally, please send me via e-mail a Word version of the Package Insert. This will help facilitate potential labeling negotiations.

Please let me know if you have any questions.

Regards,

Jason

Jason Hartman

Regulatory Project Manager

Division of Anesthesia, Analgesia and

Rheumatology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

10903 New Hampshire Ave.

Bldg 22 Rm 3171

Silver Spring, MD 20993-0002

Phone: (301) 796-2203

Fax: (301) 796-9713

E-mail: jason.hartman@fda.hhs.gov

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/s/

Lisa Basham
1/12/2007 10:50:11 AM
CSO

Incomplete Response Letter from Lee Simon, MD

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

4/16/03

NDA 21-234

Institut Biochimique SA
Attention: Larry J. Caldwell, Ph.D.
745-D Camden Avenue
Campbell, CA 95008-4146

Dear Dr. Caldwell:

We acknowledge receipt on April 1, 2002 of your March 28, 2002 submission to your new drug application (NDA 21-234) for diclofenac epolamine patch 1.3%.

I have personally reviewed the situation and your response. We do not consider this a complete response to our action letter. Therefore, the review clock will not start until we receive a complete response. The following deficiencies from our action letter still need to be addressed:

CLINICAL:

1. The submitted studies fail to demonstrate efficacy of Diclofenac Epolamine Patch (DHEP) for the treatment of the pain [redacted] On this basis, the submission is not approvable.

   a. Study 49459-01 failed to demonstrate efficacy based on the primary efficacy variables of pain intensity difference (PID), sum of pain intensity difference (SPID), pain on pressure difference (POPD) and sum of pain on pressure difference (SPOPD) for days 3, 7 and 14.

      Additional comments: The Medical Officer's original NDA review noted that the Sponsor admitted that study 01 failed on all primary efficacy endpoints. Therefore, this trial cannot be used as even supportive evidence for the efficacy of DHEP in the original NDA or any future submissions.

      Additionally, the results of this trial were published in a refereed journal eight months prior to the submission of the NDA. This paper was not referenced, acknowledged, or included in the NDA. This is a clinical and regulatory deficiency. The conclusion presented in the journal article painted DHEP in a very positive light, with no mention of the failed primary efficacy endpoints. In addition, no statistical values cited in the paper can be found in the NDA.

b. Study 49459-02 failed to demonstrate efficacy. Several deficiencies in this study are noted.

i. For study 49459-02, when the significant imbalance in body weight (an important potential confounding variable in a study with a large percentage of injuries to weight bearing areas) is incorporated in the analysis of the primary endpoint of time to pain resolution, no significant treatment difference was detected (p=0.072). Mean weight in the placebo group was 4.5 kg higher than the DHEP treated group.

Additional comments: Based upon the data in the original NDA, patients in the placebo group weighed on average 4.5 kg more than those in the DHEP group (p=0.010) which suggests a problem with randomization. In fact, the NDA statistical review commented that the any conclusion of efficacy was affected by this difference in body weight between the treatment groups.

ii. The primary endpoint, days to pain resolution is a derivative of a secondary endpoint, i.e. the daily pain score. The originally submitted analysis of daily pain score was based on a post-hoc decision to use 24-hour rather than nominal days on therapy. When the nominal day is used in the analysis, there is no statistically significant difference on any study day. The nominal day is more relevant in view of the impact of activity and weight bearing on pain following injury. Time of measurement in relation to daily sleep/rest cycle is a critical issue that should be addressed in study design and analysis.

Additional comments: The Sponsor's original protocol, according to the Medical Officer's review, had employed as a pre-specified endpoint "nominal day" to evaluate the primary and secondary endpoints. This was changed later to a 24-hour clock, however, this data analysis plan was not pre-specified in the protocol and so represents a significant protocol deviation. According to the Sponsor's reply to this deficiency, it is argued that this change does not result in any statistically significant differences. Therefore, both analysis plans do not support statistical or clinical efficacy in this study.

iii. All the secondary efficacy variables failed to show any significant difference between the treatment groups in study 49459-02. Therefore, study 49459-02 fails to provide adequate evidence for the efficacy of the patch, especially in the light of failed study 49459-01.

Additional comments: Multiple statistical and clinical trial design deficiencies occurred in this NDA as has been reviewed above.

iv. Consistency of results for secondary endpoints of average daily pain and patient as well as investigator reported global response to therapy are necessary to fully interpret the clinical benefit proposed based on the derived endpoint of median time to pain resolution.

Additional comments: By the Sponsor's own admission in study 49459-02, the outcome of the secondary measure of investigator assessment of patient's global response to treatment was not significantly different between treatments (p=0.158). Likewise, the patient's assessment of global response to treatment was not significantly different between treatments (p=0.118).

As noted in Medical Officer's original NDA review, data from four study sites was incorporated but only the contribution from the highest enroller created what nominal separation existed with this endpoint. There was no separation from placebo in the data from the other three investigators. Again, these data are not reliable to analyze secondary endpoints in this clinical trial.

OTHER DEFICIENCIES REQUIRING CORRECTION BEFORE FINAL APPROVAL:

CHEMISTRY:

1. Drug Master File (DMF) — for the drug substance diclofenac epolamine was reviewed for information on its manufacturing and controls and was found to be deficient. The DMF holder has been notified of the deficiencies.

2. The following comments pertain to the drug substance specification:
   a) Two analytical methods, HPLC and — , are used for the assay of the drug substance. Please identify only one assay method as the regulatory method.
   b) For those analytical methods that are described in the current USP, please replace Ph. Eur. methods with USP methods.

3. It is stated on page 103 of the drug product section of the original submission that the composition of the Dalin PH fragrance will be sent by the supplier —— to the FDA. Please provide a copy of the letter of authorization for the FDA to review —— DMF for Dalin PH.

4. Please provide the complete composition of the felt backing material and the release liner.

5. The inactive ingredients for which monographs exist in the USP/NF should comply with the requirements of the current USP/NF. Please provide a revised section regarding the control of the inactive ingredients.

6. Regarding in-process controls of the manufacturing of the patches, samples should be taken from —— n of the batch for the analysis of —— contents, at the completion of the ——.

7. The following information regarding drug product specification was requested from the applicant on 2/1/01 and remains deficient:

a) The patch should have some kind of identification once it is removed from the envelope. The description should contain embossed or printed identification of the patch.
b) Acceptance criteria for the upper limit of adhesive strength should be included in the specification.
c) Acceptance criteria for the drug release test (e.g., USP <724>) should be established and included in the specification.
d) Please provide two identification tests.

8. The following comments pertain to the analytical procedure and method validation for the drug substance:
   a) Please include system suitability tests in the analytical procedure for the assay of diclofenac epolamine (HPLC) and
   b) Please follow ICH Q2A and Q2B guidances for the validation of the analytical methods. The evaluation of method accuracy is recommended to be performed at a minimum of three concentration levels. Limit of detection and limit of quantitation should be included in the method validation for the impurities.

9. The following comments pertain to the stability data and stability protocol:
   a) The stability frequency described on page 269 of your stability report for the three stability batches is not acceptable. Testing frequency should be every 3 months over the first year, every 6 months over the second year, and annually thereafter.
   b) Please submit a full stability protocol that provides:
      - Selection of batches: First three production batches, and at least one production batch packaged in each container/closure system will be added to the stability program annually.
      - Storage conditions
      - Testing frequency for all batches, including annual batches, should be every 3 months over the first year, every 6 months over the second year, and annually thereafter.
      - Packaging material
      - Stability specifications, which include testing parameters and acceptance criteria.
      - Stability commitment
   c) The results for the adhesive strength test should be reported as the time retained, not simply as "comforming".
   d) The stability data should include data on drug release (e.g., USP <724>).

10. The following comments pertain to the labeling of package insert:
    a) No proprietary name has been proposed for this product
    b) The complete chemical name of diclofenac should be spelled out in the description section of the package insert. The chemical name of epolamine is incorrect.
    c) It is recommended that the inactive ingredients be listed

d) In the "How Supplied" section, the number of envelopes per carton should be specified.

11. The following comments pertain to the envelope labeling:
    a) ' — is not an approved proprietary name and should not be displayed in the envelope labeling.
    b) Please change the word ' — to "envelope."
    c) Change "The adhesive" to "The patch adhesive."
    d) It is recommended to change " 'Change patch once every 12 hours," to make it clear that only one patch is applied at anytime.

12. On the carton labeling, — is not the proprietary name for this drug product and should not be displayed as such. Please correct for the front, back, and sides of the carton labeling.

13. The following deficiencies are found in the methods validation package:
    a) The specification of the drug substance that was presented on page 3 of the methods validation package is different from what was presented on page 49 of the drug substance section in volume 2.
    b) The regulatory method for the analysis of the drug substance should be provided in detail in the methods validation package.

BIOPHARMACEUTICAL

Deficiencies:

- The pivotal biostudy (#910195) that measures exposure from the diclofenac epolamine patch does not have a complete assay validation report associated with it. It lacks information on inter- and intraday precision/accuracy, stability and recovery. This study report is of no regulatory significance in its current form and
- Study report PK-0033 lacks information on long term stability of plasma samples.
- Study PK-9814 lacks an assay validation report. The methodology and lower limit of quantification differ from Study 910195 and PK-0033.

The results from all these studies are unevaluable until the sponsor provides a complete acceptable assay validation. The results only after the assay validation has been found acceptable.

Comment:

- In the NDA the applicant has not presented any information regarding dose ranging or dose selection. As part of their re-submission the applicant should provide a rationale as to their selection of the patch size and concentration and how these factors relate to clinical efficacy/safety.

Additional comments: Considering the Medical Officer's original NDA review and the response from the Sponsor to the NA letter, it is concluded that the two "pivotal" clinical trials of DHEP failed to demonstrate significant differences compared to the placebo group. This conclusion applies to both the primary and secondary endpoints selected for these trials. The regulatory clinical comments from the non-approval letter for NDA 21-234 on October 18, 2001 were based upon scientific evidence as discussed above. Therefore, the Division cannot concur with Dr. Caldwell's comments as stated in his letter "Response to October 18, 2001 Non-Approval Letter for NDA 21-234" on March 28, 2002.

If you have any question, please call Ms. Jane Dean, RN, MSN, Regulatory Health Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Lee S. Simon, M.D.
Division Director
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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

/s/

Lee Simon
4/16/03 11:43:00 AM

Denial of Pediatric Waiver Request
11/26/01

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-234

Institut Biochimique SA (IBSA)
Attention: Larry Caldwell, Ph.D.
745-D Camden Avenue
Campbell, CA 95008-4146

Dear Dr. Caldwell:

Reference is made to your correspondence dated February 21, 2001, requesting a waiver for pediatric studies under 21 CFR 314.55(c).

We have reviewed the information you have submitted. We do not agree that a waiver is justified for diclofenac epolamine patch 1.3% for treatment of pain for the pediatric population because there is no justification for excluding pediatric patients from the trials. To state simply that DHEP is not indicated for pediatric use is not adequate. Pediatric patients are an important target population for topical NSAID products and as such should be studied in a controlled clinical trial.

Accordingly, a waiver for pediatric studies for this application is denied under 21 CFR 314.55 at this time.

If you have questions, please contact Barbara Gould, Regulatory Project Manager, at 301 827-2090.

Sincerely,

{See appended electronic signature page}

Lawrence Goldkind, M.D.
Deputy Division Director
Division of Anti-Inflammatory, Analgesic, &
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Lawrence Goldkind
11/26/01 07:42:54 PM

Post NA Action Mtg.

MEETING MINUTES

MEETING DATE: November 20, 2001 **TIME:** 10:00 a.m. **LOCATION:** Corp S300

NDA 21-234

Meeting Request Submission Date: October 18, 2001
Briefing Document Submission Date: No briefing information was submitted prior to meeting.

DRUG: Diclofenac epolamine patch 1.3%

SPONSOR/APPLICANT: Institut Biochimique SA

TYPE of MEETING: Formal Meeting in Response to Non-Approvable Letter for diclofenac epolamine patch dated October 17, 2001.

FDA PARTICIPANTS:	**Division of Anti-Inflammatory, Analgesics, & Ophthmalic Drug Products**
Larry Goldkind, MD	Medical Team Leader
Joseph Stauffer, DO	Medical Reviewer
Kent Johnson, MD	Medical Reviewer
Joel Schiffenbauer, MD	Medical Reviewer
James Witter, MD, Ph.D.	Medical Reviewer
Maria L. Villalba, MD	Medical Reviewer
Dennis Bashaw, Pharm.D.	Biopharmaceutics Team Leader
Veneeta Tandon, Ph.D.	BioPharm Reviewer
Stan Lin, Ph.D.	Biostatistics Team Leader
Suktae Choi, Ph.D.	Biostatistics Reviewer
Carmen DeBellas, R.Ph.	Chief, Project Management Staff
Barbara Gould	Project Manager
Jane Dean	Project Manager
	LPS
Daniel Feldman	Consultant

INDUSTRY PARTICIPANTS:	**Institut Biochimique SA**
Larry Caldwell, Ph.D.	US Agent

MEETING OBJECTIVE:
To discuss clinical issues identified in Non-Approval Letter dated October 18, 2001.

BACKGROUND INFORMATION:
A meeting was requested on October 19, 2001 to discuss clinical deficiencies leading to the Non-Approval (NA) Letter dated October 18, 2001. The sponsor was advised to submit a response to the deficiencies cited in the Non-Approval Letter as well as any additional questions, to the NDA in order to have a more productive meeting on November 20, 2001. The sponsor did not submit

any questions or direct response to the Non-Approval Letter deficiencies, as recommended by the Division, prior to the meeting.

DISCUSSION with FDA and DECISIONS REACHED:

Following introductions, the conversation immediately proceeded to discussion of clinical deficiencies. Dr. Caldwell stated that a full response to the NA letter would be submitted to the NDA in January 2002.

The sponsor commented:

1. Study #1 was a pilot study. The sponsor was advised at an End-of-Phase II meeting on June 16, 1998 that: "the success of the study is based on the strength of the analysis. For a clear primary analysis the sponsor should use pain alone as the endpoint". This issue led to the design a protocol for Study #2 that was submitted to the Division for review in August 1998. According to the sponsor the Division insisted that comparison of daily pain levels through time (average daily pain) be included as part of the final data analysis. The sponsor chose; however, "time to pain resolution", but not "average daily pain" as the primary endpoint with average daily pain as a non-primary endpoint.

2. Sponsor was surprised that the Division placed so much emphasis on the "secondary endpoint" of average daily pain. Patches are less convenient than taking oral NSAIDs. Once patients discontinue wearing the patch, pain measurement was not available. It is unclear how this related to the issue of average daily pain as an important endpoint. Missing data from study noncompliance can be statistically addressed.

The Division responded that it was documented in the End-of-Phase II meeting minutes that pain as a primary measure is critical to any understanding of an analgesic topical or systemic. There fore demonstration of efficacy based on a time to resolution (as defined by a pain score of less than 2 regardless of baseline or discontinuation) for the proposed indication would need to be interpreted in the context of the results of endpoints that the sponsor chose to specify as secondary. Average daily pain scores are an important aspect in understanding of the efficacy of analgesic drugs.
Sponsor commented that they never received minutes of June 1998 End-of-Phase II meeting. However, the sponsor did amend the protocol to include average daily pain and thus had demonstrated an understanding of the Division's advice given at the June 16, 1998 End-of Phase II meeting.
The sponsor stated that they did not understand how important this advice would become.

ADDITIONAL POINTS BY THE DIVISION

The Division indicated that reviews are data driven and the lack of benefit at the daily pain measurements was a significant failing in the study. The sponsor was asked if they had any validation for the use of time to pain resolution. Dr. Caldwell mentioned the Lidoderm Patch as

a possible prior where time to pain resolution was used as efficacy. It was acknowledged that time to pain resolution, or "time to exit" (PAIN, 80, 1999 533-38, reference cited here by Dr. Stauffer) was used in that trial with Lidoderm patch but this trial was testing a local anesthetic in the chronic severe pain state of post herpetic neuralgia (PHN). Drawing parallels between the mild to moderate, spontaneously resolving, pain state of strain, sprain, and contusion and the more intense neuropathic pain state of PHN should be done with caution as these two pain states are clearly different in terms of their etiology, patient population, and natural history. All are important variables in considering study designs.

The sponsor was referred to the multiple reasons cited in the NA letter for non-approval. The discussion at the meeting was in response to the sponsor's questions and comments and did not address all of the deficiencies in the NDA.
The Sponsor was advised that two pivotal trials would be needed in any future NDA given that both submitted trials failed.

ACTION ITEMS:

1. The Division will provide a copy of the June 16, 1998 meeting minutes.
2. Sponsor asked to provide literature that supports validation of pain to resolution as primary endpoint if this is to be considered in future studies.
3. Project manager will convey minutes within 30 days.

Barbara Gould
Project Manager

Concurrence Chair:

Lawrence Goldkind, MD
Deputy Director, DAAODP

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

/s/

Lawrence Goldkind
12/8/01 03:19:07 PM

Not Approvable Letter 10/18/01

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-234

Institut Biochimique SA
Attention: Larry J. Caldwell, Ph.D.
745-D Camden Avenue
Campbell, CA 95008-4146

Dear Dr. Caldwell:

Please refer to your new drug application (NDA) dated December 18, 2000, received December 19, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for diclofenac epolamine patch 1.3%.

We acknowledge receipt of your submissions dated February 05, February 22, March 16, April 12 (2), April 18 (2), May 02, May 17, June 22, August 16, and August 23, 2001.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

DEFICIENCIES LEADINGL TO NON APPROVAL

CLINICAL:

1. The submitted studies fail to demonstrate efficacy of Diclofenac Epolamine Patch (DHEP) for the treatment of the pain [redacted] On this basis, the submission is not approvable.

   a. Study 49459-01 failed to demonstrate efficacy based on the primary efficacy variables of pain intensity difference (PID), sum of pain intensity difference (SPID), pain on pressure difference (POPD) and sum of pain on pressure difference (SPOPD) for days 3, 7 and 14.

   b. Study 49459-02 failed to demonstrate efficacy. Several deficiencies in this study are noted.

      i. For study 49459-02, when the significant imbalance in body weight (an important potential confounding variable in a study with a large percentage of injuries to weight bearing areas) is incorporated in the analysis of the primary endpoint of time to pain resolution, no significant treatment difference was detected ($p=0.072$). Mean weight in the placebo group was 4.5 kg higher than the DHEP treated group.

ii. The primary endpoint, days to pain resolution is a derivative of a secondary endpoint, daily pain score. The originally submitted analysis of daily pain score was based on a post hoc decision to use 24-hour rather than nominal days on therapy. When the nominal day is used there is no statistically significant difference on any study day. The nominal day is more relevant in view of the impact of activity and weight bearing on pain following injury. Time of measurement in relation to daily sleep/rest cycle is a critical issue that should be addressed in study design and analysis.

iii. All the secondary efficacy variables failed to show any significant difference between the treatment groups in study 49459-02. Therefore, study 49459-02 fails to provide adequate evidence for the efficacy of the patch, especially in the light of failed study 49459-01.

iv. Consistency of results for secondary endpoints of average daily pain and patient as well as investigator reported global response to therapy are necessary to fully interpret the clinical benefit proposed based on the derived endpoint of median time to pain resolution.

OTHER DEFICIENCIES REQUIRING CORRECTION BEFORE FINAL APPROVAL:

CHEMISTRY:

1. Drug Master File (DMF) —— for the drug substance diclofenac epolamine was reviewed for information on its manufacturing and controls and was found to be deficient. The DMF holder has been notified of the deficiencies.

2. The following comments pertain to the drug substance specification:
   a) Two analytical methods, HPLC and — , are used for the assay of the drug substance. Please identify only one assay method as the regulatory method.
   b) For those analytical methods that are described in the current USP, please replace Ph. Eur. methods with USP methods.

3. It is stated on page 103 of the drug product section of the original submission that the composition of the Dalin PH fragrance will be sent by the supplier —— .o the FDA. Please provide a copy of the letter of authorization for the FDA to review —— DMF for Dalin PH.

4. Please provide the complete composition of the felt backing material and the release liner.

5. The inactive ingredients for which monographs exist in the USP/NF should comply with the requirements of the current USP/NF. Please provide a revised section regarding the control of the inactive ingredients.

6. Regarding in-process controls of the manufacturing of the patches, samples should be taken from [redacted] of the batch for the analysis of [redacted] contents, at the completion of the [redacted]

7. The following information regarding drug product specification was requested from the applicant on 2/1/01 and remains deficient:
   a) The patch should have some kind of identification once it is removed from the envelope. The description should contain embossed or printed identification of the patch.
   b) Acceptance criteria for the upper limit of adhesive strength should be included in the specification.
   c) Acceptance criteria for the drug release test (e.g., USP <724>) should be established and included in the specification.
   d) Please provide two identification tests.

8. The following comments pertain to the analytical procedure and method validation for the drug substance:

   a) Please include system suitability tests in the analytical procedure for the assay of diclofenac epolamine (HPLC) and
   b) Please follow ICH Q2A and Q2B guidances for the validation of the analytical methods. The evaluation of method accuracy is recommended to be performed at a minimum of three concentration levels. Limit of detection and limit of quantitation should be included in the method validation for the impurities.

9. The following comments pertain to the stability data and stability protocol:
   a) The stability frequency described on page 269 of your stability report for the three stability batches is not acceptable. Testing frequency should be every 3 months over the first year, every 6 months over the second year, and annually thereafter.
   b) Please submit a full stability protocol that provides:
      - Selection of batches: First three production batches, and at least one production batch packaged in each container/closure system will be added to the stability program annually.
      - Storage conditions
      - Testing frequency for all batches, including annual batches, should be every 3 months over the first year, every 6 months over the second year, and annually thereafter.
      - Packaging material
      - Stability specifications, which include testing parameters and acceptance criteria.
      - Stability commitment
   c) The results for the adhesive strength test should be reported as the time retained, not simply as "comforming".
   d) The stability data should include data on drug release (e.g., USP <724>).

10. The following comments pertain to the labeling of package insert:

a) No proprietary name has been proposed for this product.

b) The complete chemical name of diclofenac should be spelled out in the description section of the package insert. The chemical name of epolamine is incorrect.
c) It is recommended that the inactive ingredients be listed
d) In the "How Supplied" section, the number of envelopes per carton should be specified.

11. The following comments pertain to the envelope labeling:
    a) is not an approved proprietary name and should not be displayed in the envelope labeling.
    b) Please change the word to "envelope."
    c) Change "The adhesive" to "The patch adhesive."
    d) It is recommended to change to "Change patch once every 12 hours," to make it clear that only one patch is applied at anytime.

12. On the carton labeling. s not the proprietary name for this drug product and should not be displayed as such. Please correct for the front, back, and sides of the carton labeling.

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    a) The specification of the drug substance that was presented on page 3 of the methods validation package is different from what was presented on page 49 of the drug substance section in volume 2.
    b) The regulatory method for the analysis of the drug substance should be provided in detail in the methods validation package.

BIOPHARMACEUTICAL

Deficiencies:

- The pivotal biostudy (#910195) that measures exposure from the diclofenac epolamine patch does not have a complete assay validation report associated with it. It lacks information on inter- and intraday precision/accuracy, stability and recovery. This study report is of no regulatory significance in its current form an
- Study report PK-0033 lacks information on long term stability of plasma samples.
- Study PK-9814 lacks an assay validation report. The methodology and lower limit of quantification differ from Study 910195 and PK-0033.

The results from all these studies are unevaluable until the sponsor provides a complete acceptable assay validation. The results only after the assay validation has been found acceptable.

Comment:

- In the NDA the applicant has not presented any information regarding dose ranging or dose selection. As part of their re-submission the applicant should provide a rationale as to their selection of the patch size and concentration and how these factors relate to clinical efficacy/safety.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

Sincerely,

{See appended electronic signature page}

Larry Goldkind, M.D.
Deputy Division Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

Institut Biochimique SA (IBSA)
745-D Camden Avenue
Campbell, CA 95008-4146

2. TELEPHONE NUMBER *(Include Area Code)*

(408) 871-7331

3. PRODUCT NAME

DHEP Patch (Diclofenac Epolamine 1.3%)

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER

4053

6. LICENSE NUMBER / NDA NUMBER

N021234

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO *(See reverse side if answered YES)*

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Larry J. Caldwell Larry J. Caldwell, Ph.D.	Research Director US Representative of IBSA	11/6/00

FORM FDA 3397 (5/98)

First Cycle October 11, 2001

M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION CENTER
FOR DRUG EVALUATION AND RESEARCH

EVALUATION OF CLINICAL INVESTIGATOR INSPECTIONS.

DATE:	October 11, 2001
NDA	21-234
HFD	550
SPONSOR:	Institut Biochimique SA
Product:	diclofenac epolamine patch
Type:	2
Potential:	S
Indications:	For the treatment of pain [redacted]
Project Manager:	Barbara Gould
Medical Officer:	Joseph Stauffer

I. Background:

These routine inspections were part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which NDA 21-234 approval may be based and to assure that the rights and welfare of the human subjects of those studies were protected. These inspections were conducted in accordance with CP 7348.811, Clinical Investigators, in addition to concentrate in comparing source documents, case report forms (CRFs), and data listings in regard to primary endpoints, adverse drug events reporting and discontinued subjects in these protocols. Sites selected in corroboration between HFD-550 Division medical officer, Dr. Boyd and DSI reviewer, Dr. Jose Carreras.

Name	City	Protocol	CL
[redacted]	Chicago, Illinois	# N49,459-2	VAI
Michael C. Rowbotham, M.D.	San Francisco, California	# N49,459-2	VAI
Bradley S. Galer, M.D.	Chadds Ford, Pennsylvania	# N49,459-2	VAI
[redacted]	Madison, Wisconsin	# N49,459-2	VAI

In addition because this product is a NME a Sponsor/Monitor inspection was conducted using the data from Dr. Richard Lewis of Sacramento, California.

[redacted]	Irvine, California	Sponsor/Monitor	NAI*

#1

Dr. —

This investigator enrolled 115 subjects in the study. Ninety-two subjects completed. The field investigator examined eighty-one records in depth. Inspectional findings were not clinically significant to preclude the use of the data in support of this application.

Site #2

Dr. Rowbotham

This investigator enrolled one hundred and sixty-five subjects in the study. One hundred and fifty nine subjects completed the study. Seven subjects were lost to follow-up. The field investigator examined twenty records in depth. Inspectional findings were not clinically significant to preclude the use of the data in support of this application.

Site #3 Dr. Galer

This investigator enrolled 43 subjects in the study. Two subjects were discontinued in favor of other therapy, two subjects were lost to follow-up. The field investigator examined all records in depth. Inspectional findings were not clinically significant to preclude the use of the data in support of this application.

OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS:

No objectionable conditions were found in the above sites, which would preclude the use of the data submitted in support of pending NDA.

Jose A. Carreras, M.D.

cc:
NDA 21-234
Division File
HFD-47/Currier

S Schmidt - 550

1

MEETING MINUTES

MEETING DATE: March 28, 2000 **Time: 1:00** **Location: S300**

IND 49,459 **Request Receipt Date:** 2-1-00
Briefing Doc. Received: 3-13-00

DRUG: Diclofenac Epolamine Patch

SPONSOR: Institut Biochimique S.A.

TYPE of MEETING: Pre NDA

FDA PARTICIPANTS:
Karen Midthun, M.D., Division Director, Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products
Christina Fang, M.D., Medical Officer
Mona Zarifa, Ph.D., Chemistry Team Leader
Sue-Ching Lin, R.Ph., Chemistry Reviewer
Tracey Zoetis, Ph.D., Pharmacology Reviewer
Stan Lin, Ph.D., Statistical Team Leader
Suktae Choi, Ph.D., Statistical Reviewer
Dennis Bashaw, PharmD, Team Leader Pharmacokinetics
Sue-Chih Lee, Pharmacokinetics Reviewer
Sharon Schmidt, Project Manager
Leslie Vaccari, Acting Chief Project Management Staff

INDUSTRY PARTICIPANTS:
Pino Mautone, R&D Manager, IBSA
Eleonora Tajana, Clinical Research Manager, IBSA
Larry Caldwell, Project Manager

Gail Sheirbon, Document Controller
Ryoji Konishi, Executive Director, Teikoku Seiyaku
Keiji Masaki, Manager of QA, Teikoku Seiyaku

BACKGROUND:
On February 1, 2000, the sponsor met with the FDA to discuss aspects of their electronic submission for their NDA. At that meeting FDA recommended that the sponsor have a preNDA meeting to discuss the substance of their NDA, in particular have they addressed the issues raised in the End-of-Phase 2 meeting held June 16, 1998. The present meeting is in response to that request.

DISCUSSION: Following introductions, initial comment by the FDA was made followed by a discussion of the questions listed in the briefing document.

Initial FDA Comments:

FDA commented with regard to the two studies (49459 and 49459-2) that the sponsor has identified as pivotal for demonstrating efficacy in

It is not completely clear what the specific indication(s) are. FDA requested draft labeling be submitted, including the "Indication" and the "Dosage and Administration" sections. The sponsor clarified that they plan to limit the indication at this time to analgesia. Draft labeling will be provided to the FDA as soon as possible.

As discussed in the June 16, 1998, End-of-Phase 2 meeting, the pre-specified analysis in the protocol for Study 49459 did not show a positive result. In general, results of post-hoc analysis are used for exploratory purposes and are not acceptable as substantial evidence of efficacy. Furthermore, the proposed post-hoc analyses are inadequate. In the June 1998 meeting, the FDA indicated that at least one more efficacy study should be conducted. If the results of the second study 49459-2 are very strong, it is possible that the first study, No. 49459, could be supportive. However, FDA has significant reservations regarding the ability of the first study to be supportive, given that it failed on both primary endpoints at all three time-points, and that the endpoint differed between the two studies. FDA noted that the March 13, 2000 briefing document submitted by the sponsor indicated that there were four primary efficacy measures, but only measures #1 (PID) and #3 (POPD) were designated as primary endpoints and both had failed. FDA recommended that a third study be performed.

The sponsor noted that if the second study gave a very strong positive result, then they might re-analyze the first study, using time to resolution of pain as the endpoint. FDA noted that this was problematic, given its post-hoc nature.

Sponsor's Questions Followed by FDA Responses:

1. Does the NDA contain sufficient information to satisfy filing requirements for Pharmacology and Toxicology?

   a) *Summary of Sponsor's Proposal:*
   Submission of Segment 2 teratology and Segment 3 reproduction studies, as suggested in the June 10, 1998 End of Phase 2 meeting are planned.

   FDA Response:
   This is a reasonable plan.

   b) *Summary of Sponsor's Proposal:*
   The sponsor plans to submit a 28-day dermal toxicity in rabbits, with pharmacokinetic data. Animal studies have not been performed in recent years because of extensive human experience in European markets.

FDA Response:
The sponsor should demonstrate that both local and systemic toxicity have been characterized for DHEP. The 28-day dermal study in rabbits should characterize local toxicity; however, it will not address systemic toxicity since evaluation of all relevant parameters was not performed. The 13-week oral studies in dogs and rats should address the systemic toxicity. The sponsor should use the pharmacokinetic data from both the systemic and local toxicity studies to demonstrate the bridge to human pharmacokinetic data and relevant exposure levels.

c) *Summary of Sponsor's Submission:*
The sponsor does [redacted] or

FDA Response:
FDA acknowledged the sponsor's plan. [redacted]

d) *Summary of Sponsor's Submission:*
The drug absorbs light at [redacted] nm, light penetrates the patch, and drug remains on or in the skin after removal of the patch. The sponsor indicated that they have addressed the issue of phototoxicity with a clinical study. [However, FDA noted that the clinical study conducted was described as a "Photoallergy Maximization Test" (see item 3 below).]

FDA Response:
It is reasonable to address the issue of phototoxocity in a clinical study, but a photoallergy study is not sufficient for this purpose. The sponsor stated that they would conduct a phototoxicity study in humans in response to this FDA comment [redacted]

e) *Summary of Sponsor's Submission:*
The sponsor plans to submit all available information on epolamine and /or DHEP in the NDA filing. The finished product was used for the 28-day dermal study in rabbits.

FDA Response:
This is a reasonable plan. FDA provided the sponsor with the draft guidance on dermal safety issues for nonclinical studies.

2. Does the NDA contain sufficient information to satisfy the filing requirements for pharmacokinetics?

a) Assessment of in vitro release:
The sponsor indicated that their method will be similar to that for lidocaine patch.

FDA Response:
We need a more detailed description of the method and specification. The method and specification should be such that lot-to-lot variations can be discriminated.

b) Residual patch contents (*in vivo*)

FDA Response:
FDA noted that the study has been conducted to determine the residual diclofenac after 12-hour application in humans. FDA noted that the number of subjects and site of application (the latter can affect the release of diclofenac from the patch) was not provided.

The FDA stated there needed to be a minimum of six subjects in this study. The sponsor responded that either twelve or twenty subjects were used in that study and the information will be included in the application.

c) Site of application:
The patch is generally applied to torso or on limb joints. The PK studies utilized either skin on the back or on the inner side of the arm. The sponsor considers it unnecessary to explore other sites because of the "extremely low blood levels of diclofenac found in the existing studies."

FDA Response:
FDA needs to know what kind of plasma levels were actually observed in those studies. Generally, the sponsor should include application sites that will be expected to have greater absorption.

d) Accounting of the epolamine:

FDA Response:
FDA noted that the studies about the fate of epolamine were only conducted in rats. We reserve comment on the adequacy of this study until the study can be reviewed. The sponsor should submit metabolic/pharmacokinetic data in humans to support the safety of epolamine.

e) Exercise induced changes in absorption:

FDA Response:
The sponsor did not evaluate exercise-induced changes in absorption because the patch is not suited to application on sweaty skin. Since increased absorption of diclofenac during exercise is anticipated and some patients may be creative in making sure that the patch stays on, FDA strongly recommends that the sponsor conduct such a study.

3. Does the NDA contain information sufficient to satisfy filing requirements for safety in human studies?

FDA Response:
ICH guidelines (at least 300 subjects for six months and short term exposure in 1500 subjects) need to be followed. The sponsor indicates that they have chronic safety data available, and that it is "fairly comprehensive for the territory of Switzerland." Please clarify what type of data is available, and how the data were collected. Safety data from sources other than clinical trials should be organized, summarized, and presented in a format consistent with data from clinical trials.

The sponsor indicated that they had data for 1500 individuals at any exposure, but that they had no chronic use safety data. The data from Switzerland is pharmacovigilance data. The sponsor noted that although the product is approved for osteoarthritis in several European countries, it is to be used only for up to 10 day, e.g. in the setting of an acute flare. FDA noted that the sponsor should provide more detail regarding the type of safety data available so that FDA could assess the adequacy.

The to-be-marketed formulation needs to be studied for 1) irritation, 2) phototoxicity, 3) photoallergy, and 4) contact sensitization. FDA recommended that the sponsor submit a summary of the dermal safety information to the IND (in advance of the NDA submission), so that it can forwarded for consult to the Division of Dermatology and Dental Products.

Additional FDA Comments:

1. The pediatric rule must be addressed. It is very likely that diclofenac epolamine patch will be used for children [redacted]. It is not clear what the plan is to address this issue. The use of the patch in children needs to be studied to provide adequate dosing and safety information. The sponsor may want to consider performing a pediatric efficacy study to serve as an additional basis of substantial evidence for efficacy.

2. FDA inquired whether the sponsor had any questions regarding chemistry. The sponsor noted that they had some questions regarding specifications for drug release and indicated that they planned to do something similar to the Lidoderm Patch. They noted that they would have stability data for approximately 1½ years. FDA noted that this should be acceptable. FDA provided the sponsor with the suggested format for the CMC section and suggested a follow-up telephone conference for CMC issues.

CONCLUSIONS:

The FDA closed the meeting by stating its continued reservations regarding the ability of Study 49459 to contribute to the substantial evidence of efficacy needed for the product, and again stated its recommendation to perform a third efficacy study.

ACTION ITEMS:

1. The sponsor will discuss their proposal for providing substantial evidence of efficacyand update the FDA.

2. The sponsor should provide more detail regarding the number of subjects exposed to the patch in clinical studies and from other sources by duration of exposure. (FDA does not have sufficient information to assess the adequacy of the safety database.)

3. Clinical studies to assess irritation, phototoxocity, photoallergy, and contact sensitization are needed.

4. The sponsor needs to address the pediatric rule.

5. FDA recommends that the sponsor request a telephone conference to ensure that CMC issues are adequately addressed.

Drafted by:
Sharon Schmidt

Revised by: 5-25-00
Leslie Vaccari

Concurrence : 5-29-00
Karen Midthun, M.D.
Division Director

cc:Original IND 49,459
HFD-550/Division File
HFD-550/Bashaw
HFD-550/Midthun
HFD-550/CFang
HFD-550/SSchmidt
HFD-550/LVaccari
HFD-550/MZarifa
HFD-550/Sue-ChingLin
HFD-550/StLin
HFD-550/SChoi
HFD-550/Sue-ChihLee

MEETING MINUTES

MEETING MINUTES

Meeting Date: February 1, 2000 Time: 1:00 Location: S300

IND 49,459

Date of Meeting Request: 1-4-00
Date Sponsor Requested: end Jan./beg. Feb
Briefing Document Submission Date: 1-18-00

Drug: Diclofenac Epolamine Patch
Sponsor : Institut Biochimique
Indication: Pain in Minor Sports Injury

Type of Meeting: pre-NDA meeting to discuss electronic submission

FDA Participants: Karen Midthun, Division Director; Christina Fang, Medical Officer; Mona Zarifa, Acting Chemistry Team Leader; Stan Lin, Statistical Team Leader; Suktae Choi, Statistician; Asoke Mukherjee, Pharmacologist; Andrea Weir, Pharm/Tox Team Leader; Leslie Vaccari, Acting Supervisory Project Manager; Sharon Schmidt, Project Manager

Industry Participants: Larry J. Caldwell, Ph.D., Consultant/Representative of Sponsor; _____ Statistician for Sponsor: _____, Consultant; Francisco Bejar, Regulatory Associate

Meeting Objective: To clarify reviewer needs for the electronic and paper copy of the NDA

Background Information: The sponsor intends to submit an NDA for a pain indication within the next 3 months. An EOP2 meeting was held in June 1998.

1. **Should the manufacturing process validation be included inside the CMC in the same section as process controls?**

   Yes. Text information on The Manufacturing Process Validation and in-Process Controls should be included in the section entitled Methods of Manufacturing and Packaging and should be properly subdivided into subsections with the proper subtitle. The data summary should be in the Controls section. The batch records should be put in a separate section or volume of the NDA.

2. **The drug substance is manufactured by _____ They plan to submit a drug master file to the Agency approximately at the**

same time as our filing the NDA. Should the DMF come to the same reviewers as the NDA? Would the Agency prefer to see the DMF copied into the electronic filing of the NDA?

The DMF is maintained as a separate file from the NDA because of its proprietary nature, and should be submitted as a paper copy. Once the DMF is submitted, the reviewers will be able to access the DMF. The company that submits the DMF should provide a letter of cross-reference. We encourage that the DMF be submitted well before the NDA and as soon as possible.

3. **There is an electronic section called "Summary". In the past, the Agency has not always required an "overall" summary. Does the Agency want an "overall" summary?**

Yes.

4. **There are many clinical reports of safety and effectiveness from Europe in this filing, mainly in support of the product safety. Does the Agency wish to receive all of the case report data listings (scanned) from these older studies?**

Yes. The data should be summarized in formats consistent with the U.S. study summaries. Please use the COSTART term system and not the WHO terms for the summary of adverse events.

5. **Guidelines refer to "Review Aids" – what are these?**

Review Aids are discs or electronic files that contain information already found the archival copy but in a different format. These should be clearly marked "REVIEW AIDS – NOT FOR ARCHIVE" and included in the appropriate technical section of the review copy.

If you have any more questions in this regard, please feel free to call the Project Manager, Sharon Schmidt at 301-827-2536.

6. **Publications (Foreign) – Do foreign reports scanned into the computer need bookmarks within the documents. Also foreign reports?**

Yes, bookmarks are needed. As a reminder foreign reports and literature that are part of the NDA must be translated into English before being included in the NDA. Any foreign literature/reports that include safety data should be translated and included in the NDA.

7. **The Guidelines state that different reviewers have different requirements for electronic submissions in regards to with and without paper copies. Exactly what does each reviewer require to aid in the expeditious review of their portion of the NDA? We would like individual reviewer input.**

Biopharm - Would like a paper copy of the PK section. The PK summary should be in Word and tables in Excel.

Medical – Would like a paper copy of the clinical study reports and major tables or appendices on group data; the line listings on individual patients can be in electronic format only.

Pharmacologist - Would like a paper copy of the Pharm/Tox section.

Chemist - Would like a paper copy of the CMC section.

Statistics – Would like the same as the Medical Officer, with data in SAS transport format.

The Division requested 12 reviewer copies of the 1.1 volume of the NDA.

8. **Individual Case Report Forms will be submitted in paper. Any specific instructions regarding them (outside of the standard filing format)?**

The Division received clarification from the sponsor that the CRFs would be submitted in paper format only (i.e., not electronically). The standard format should be used.

9. **Is the electronic review copy in any way different from the archival copy?**

They should be identical, with the exception of some format differences (e.g. reviewer aids).

10. **Guidelines refer to "Field Copy"? What is this?**

It is the paper copy of the CMC section sent to the "field" or district office for CMC inspection purposes.

11. **Is there any procedure for electronic signatures?**

No, not at this time. Please submit a paper copy of those documents that require original signatures.

12. **Labeling: Does the Agency want to see currently used foreign packaging and labeling, or just what is proposed for the US?**

The Division indicated that it would like to see all the labels that are presently in use worldwide and would like to see 2-3 of these labels translated into English. After some discussion with the sponsor, the Division agreed that the sponsor

the datasets to be provided and the data elements that should be included in each dataset.

In addition to electronic datasets, study data collected for individual patients, organized by time, can be provided in PDF files. We call this collection of data a patient profile, and it serves as an adjunct to the electronic datasets.

We would like to discuss the general organization and content of the CRT data sets and any additional data sets suitable for reproducing the confirming analyses. Would it be preferred that patient profiles be included in the submission?

Yes, for patients who had serious adverse events and discontinued the study.

17. **Is it preferred to submit programs that you used in your statistical analysis software to arrive at the final analysis for principal efficacy and safety data?**

Yes, the raw data should be submitted and please provide the program that was used to derive the variables and document how the variables were derived.

What is the perceived relationship of the datasets required for the analyses to the CRT datasets.

The CRTs are SAS transport datasets that correspond to different CRF domains. To facilitate clinical/statistical review, the efficacy CRT for each study should contain complete data from all patients recruited for the study. It contains the raw data transcribed from the CRFs as well as any subsequently derived variables.

18. **We would like to discuss the following general consideration for datasets as it applies to the CRT and analyses data sets:**

6. General considerations for datasets
The efficient use of datasets by the reviewer can be significantly improved if some basic principles are followed in setting up the datasets.

Are each of the CRT data sets to contain the study, center/site, treatment assignment, sex, age, and/or race of the subjects?

Yes.

Are each of the CRT data sets to be printable?

Yes. The data sets in SAS transport should automatically be printable.

Additional comments:

The Division noted that the subject of today's meeting had been on the format of submission for the NDA. The Division asked whether the sponsor intended to have a pre-NDA meeting to discuss the substance of the NDA. The Division indicated that it was unclear how the issues raised in the End-of-Phase 2 meeting held on June 16, 1998, had been addressed. The Division recommended a pre-NDA meeting to discuss the content of the NDA and noted that a summary of the different sections to be included in the NDA should be submitted as meeting materials. Dr. Caldwell, the sponsor's representative, stated that he did not think that such a meeting would change the sponsor's decision to submit the NDA. The Division asked if this would be the case, even if refuse-to-file issues were identified. Dr. Caldwell noted that he would take the Division's recommendation under advisement.

Action Items:

1. The Division agreed to set up a telephone conference in 7-10 days to provide the sponsor with further clarification on the CRTs.

2. The sponsor will provide summaries of each discipline's section of the NDA for the FDA's comment prior to submitting their NDA in April/May 2000. Specifically they will provide reasons for why certain pharm/tox studies requested in the EOP2 meeting (June 16, 1998) were not needed. They will also provide preliminary information on ongoing clinical studies.

Addendum:

Subsequent to the February 1, 2000, meeting, the sponsor agreed to schedule a pre-NDA meeting for March 28, 2000, to discuss the substance of the proposed NDA.

Sharon A. Schmidt 3/2/00
Sharon Schmidt, Project Manager

Karen Midthun 3/2/00
Concurrence Chair:
Karen Midthun, M.D., Division Director

CC: IND 49,459
Div. File
HFD-550/S.Schmidt/K.Midthun/C.Fang/M.Zarifa/S.Lin/S.Choi/A.Mukherjee
/A.Weir /L.Vaccari

Meeting Minutes

Type of Meeting: Sponsor Meeting

IND: 49,459 Diclofenac Epolamine Patch (DHEP)

Sponsor: Institut Biochimique SA.

Date: June 16, 1998

Attendees
FDA: R Delap / J Hyde, C Yaciw, D Bashaw, S Lin, A Weir, V Lutwak,
Institut Biochimique: L Caldwell, E Tajana, P Mautone

Background: See premeeting minutes.

CMC
Division: There were no CMC issues with the premeeting package.
Sponsor: They are working on the validation package and will follow the CMC guidance.

2. Does IND 49,459 contain information sufficient to satisfy filing requirements for Pharmacology and Toxicology? (See entire section 8 of the IND, as well as section 9, report A.)

If not, then what additional information is required?

Ans.2
For any indication, the following should be conducted with DHEP.

- Segment 2 reproductive toxicity in rabbit
- Segment 3 reproductive toxicity in rat

For [redacted] indication (short-term)

- Dermal 28 day will support up to 2 weeks use for an NDA

Phototoxicity: More information is needed to assess need for phototoxicity

- Does the drug/inactives absorb light at 280-700 nm?
- Does light penetrate the patch?
- Does drug remain in/on skin after the patch is removed?

Request for information:

- All available information on epolamine and/or DHEP
- Were all excipients listed on page 00015 tested in the dermal toxicity study described on page 00018?
-

Clarification: Division: The sponsor should provide information either from published studies, literature, or studies to address the issue defined above. Phototoxicity concerns are with the drug product. The sponsor was assured that if the paste/inactives doesn't absorb light at 280-700 nm, they wouldn't need further studies.

3. Does IND 49,459 contain information sufficient to satisfy the filing requirements for pharmacokinetics? (See section 9, reports B and C.)

   If not, then what additional information is required?

- Assessment of release (in vitro)
- Residual patch contents
- Site of application (in vivo)
- Accounting of the epolamine (PK) (biologic fate)
- Exercise induced changes in absorption

Clarification: The sponsor should be clear in their labeling which type of skin the patch would be used on: unbroken or broken. The sponsor should provide studies to evaluate changes in absorption during exercise. The sponsor should use a standard US population including African Americans for their studies. Last, we encourage the sponsor to share their development plans with the division for comment before beginning their studies.

1. Does the Agency agree with the sponsor's opinion, that the sports injury clinical report represents one "adequate and well-controlled" pivotal study for efficacy in minor sports injury?

   If not, then what are the specific shortcomings of this study?

Answer: Yes, the design was generally adequate, but we do not feel the study showed a positive result. There should be a clearcut primary analysis.

Clarification: After a discussion of the choice of analgesic model and sample size of each arm, the division requested any available information on the ——— The sponsor may need more that the usual standard sample size(50/arm) to show effect.

The success of the study is based on the strength of the analysis. For a clear primary analysis the sponsor should use pain alone as the endpoint.