

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204623Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA:	204623
Brand Name:	PENNSAID 2%
Generic Name:	Diclofenac sodium topical solution 2%
Indication:	Treatment of [REDACTED] (b) (4) osteoarthritis of the knee(s)
Dosage Form:	Solution
Strengths:	40 mg/2 mL
Route of Administration:	Topical
Dosing regimen:	2 mL (40 mg)/knee twice daily
Applicant:	Mallinckrodt Inc.
OCP Division:	DCP2
Clinical Division:	DAAAP (OND-170)
Submission Date:	August 7, 2013
Reviewers:	Ying Fan, Ph.D.
Team Leader:	Yun Xu, Ph. D.

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1 EXECUTIVE SUMMARY

Mallinckrodt Pharmaceuticals submitted a response to the Complete Response action letter for NDA 204623 issued on March 4, 2013, and is seeking approval of PENNSAID 2% w/w topical solution 2 mL (40 mg)/knee twice daily for treatment of (b) (4) osteoarthritis of the knee(s).

1.1 Recommendations

The Office of Clinical Pharmacology finds the NDA 204623 acceptable from a Clinical Pharmacology perspective.

1.2 Phase IV commitments

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics findings

This is a resubmission of NDA 204623, diclofenac sodium topical solution 2% w/w, in response to the Complete Response (CR) action letter on March 4, 2013. The clinical pharmacology related item cited in the CR letter was the lack of reserve samples retained at the clinical site for the bioavailability studies. This resubmission includes a new relative bioavailability study, MNK15310250, to resolve this deficiency.

Relative Bioavailability

The relative bioavailability of diclofenac was evaluated in three multiple dose PK studies (Study COV05100070, Study COV05100175, and Study MNK15310250). Two of them (Study COV05100070, Study COV05100175) were submitted in the original NDA 204623. Based on the OSI memo dated December 18, 2012, due to the lack of reserve samples, the authenticity of test and reference drug products administered can not be confirmed for both studies. Therefore, the data from these two studies can not be accepted for further Agency's review (see the original NDA review dated 01/28/13 in Darrrts and in Appendix of this review). This review focuses on the new relative bioavailability study MNK15310250 in current resubmission.

Study MNK15310250 is a randomized, single center, open-label, multiple-dose, two-way crossover study, comparing PENNSAID 2% topical solution and PENNSAID 1.5% topical solution. The PK results are summarized in Table 1.1. Because the PENNSAID 2% formulation is intended for chronic use, it is more relevant to compare the systemic exposure at steady state. At steady state on Day 8, the systemic exposure for PENNSAID 2% formulation is higher than PENNSAID 1.5% formulation. The BE analysis result between PENNSAID 2% topical solution and PENNSAID 1.5% topical solution on Day 8 can be found in Table 1.2. The results show that the AUC_{0-12} and C_{max} value from PENNSAID 2% topical solution at steady state was 49% and 46% higher compared to PENNSAID 1.5% topical solution, respectively.

For the comparison of PENNSAID 2% topical solution to the oral diclofenac sodium tablet, as the data from Study COV05100070 are considered unacceptable (OSI failed), systemic exposure of diclofenac following oral administration of a single dose of 50 mg diclofenac sodium was also obtained from NDA 20947 (PENNSAID 1.5%) reviewed by Dr. David Lee dated 7/1/2009 in Darrrts. Following oral administration of a single dose of 50 mg diclofenac sodium, the systemic exposure of diclofenac from NDA 20947 review were 6300 ng•h/mL for AUC_{0-inf} and 1500-1600 ng/mL for C_{max} . In Study COV05100070 which failed OSI inspection, diclofenac AUC_{0-24} and C_{max} were (b) (4) ng•h/mL and

(b) (4) ng/mL, respectively, following oral administration of 75 mg diclofenac sodium BID at Day 1. Based on the results from both studies, it is reasonable to conclude that the systemic exposure of diclofenac following PENNSAID 2% topical solution at the steady state on Day 8 will be much lower compared to that following oral diclofenac sodium tablet.

Table 1.1. Summary of Day 8 (Steady State) Diclofenac Pharmacokinetic Parameters Comparison

	Study MNK15310250 (n=25)		Study COV05100070 (n=30) (OSI failed)	From Dr. David Lee's Review for NDA 20947
Parameters Mean (SD)	PENNSAID 2% Topical solution 40 mg/knee BID	PENNSAID 1.5% Topical solution 19.3 mg/knee QID	Diclofenac Sodium Tablet 75 mg BID	Diclofenac Sodium Tablet 50 mg (Single dose)
Day 1				
AUC ₀₋₁₂ (ng•h/mL)	77.27 (49.89)	27.46 (23.97)	(b) (4)	6300 (AUC _{0-inf})
C _{max} (ng/mL)	12.16 (7.66)	2.30 (2.02)	(b) (4)	1500-1600
Day 8				
AUC ₀₋₁₂ ^{SS} (ng•h/mL)	204.58 (111.02)	141.49 (92.47)	(b) (4)	NA
C _{max} ^{SS} (ng/mL)	25.24 (12.95)	17.04 (11.28)	(b) (4)	NA

Table 1.2 BE analysis results on Day 8 in Study MNK15310250

Parameter	PENNSAID 2%	PENNSAID 1.5%	Ratio, 90% CI
C _{max} ^{SS} (ng/mL)	25.24	17.04	145.68 (125.35-176.35)
AUC ₀₋₁₂ ^{SS} (ng h/mL)	204.58	141.49	149.162 (123.16-180.66)

In conclusion, diclofenac AUC₀₋₁₂ and C_{max} value from PENNSAID 2% topical solution at steady state were 49% and 46% higher compared to those from PENNSAID 1.5% topical solution, respectively, at steady state on Day 8, and they are much lower compared to those from oral diclofenac tablet.

2 QUESTION BASED REVIEW

2.1 General Attributes/Background

2.1.1 What is the pertinent regulatory background of PENNSAID 2%?

PENNSAID (diclofenac sodium topical solution) 1.5% was approved in November 2009 under NDA 20947 for the treatment of signs and symptom of OA of the knee (s). Mallinckrodt Pharmaceuticals submitted the original 505 (b)(2) new drug application NDA 204623 for PENNSAID (diclofenac sodium topical solution) 2% in a metered-dose pump (b)(4) and administered BID as alternative to the QID dosing of PENNSAID 1.5% on May 4, 2012. The original NDA contains two relative bioavailability studies (COV05100070 and COV05100175) and one 4-week efficacy and safety study. Agency issued a Complete Response (CR) Letter on March 4, 2013. The main deficiency from a Clinical Pharmacology perspective is the finding from the Office of Scientific Investigations (OSI) that the reserve samples were not retained at the clinical site for the two relative bioavailability studies (COV05100070 and COV05100175) so the results cannot be used. The letter stated that the sponsor must conduct a new relative bioavailability study using diclofenac sodium topical solution PENNSAID 2%. The language in the CR letter is as follows:

“The Office of Scientific Investigations (OSI) found that, for Studies COV05100070 and COV05100175, reserve samples were not retained at the clinical site. As a result, the authenticity of the test and reference drug products administered at the clinical site could not be confirmed and data from this site were not acceptable for review. To resolve this deficiency, you must conduct a new relative bioavailability study using diclofenac sodium topical solution, 2% and PENNSAID.”

In the EOP2 meeting, the Division indicated that the sponsor need to conduct a 12-week clinical efficacy study for the proposed PENNSAID 2% formulation. However, the Sponsor conducted a 4-week study instead when the NDA was submitted, and referred to the OGD guidance of PENNSAID 1.5% formulation (NDA 20947) to support their position that the 4-week study is sufficient.

According to the OGD Draft Guidance, two *in vivo* studies are recommended: a single-dose, two-way crossover pharmacokinetics study in healthy subjects to demonstrate bioequivalence on systemic exposure between the innovator and the generic, and a 4-week randomized, double blind, parallel, placebo-controlled clinical trial in osteoarthritis patients to demonstrate bioequivalence on clinical efficacy endpoints.

At the filing meeting of the original NDA, the Division decided to consider the sponsor’s rationale during the review process. In addition, the Division thought the PK data may be sufficient to support approval in lieu of clinical efficacy data, based on the fact that PENNSAID 2% topical solution showed a comparable systemic exposure compared to PENNSAID 1.5% topical solution. Therefore, the relative bioavailability study between the PENNSAID 2% topical solution and PENNSAID 1.5% topical solution could be considered pivotal; OSI inspection was requested on both relative bioavailability Studies COV05100170 and COV05100175.

Before the wrap-up meeting of the original NDA, the Division has determined that the 4-week efficacy study will be acceptable, and efficacy of the product can be supported by a 4-week efficacy study. Therefore, the PK study would just be supportive and not pivotal. Considering that the OSI inspection results were unacceptable, the study results could not be used to support the NDA application. Therefore, complete response was given to the sponsor, even if the relative bioavailability studies were finally

determined as not pivotal.

When the sponsor resubmitted the new relative bioavailability study in this re-submission, an OSI inspection will not be needed at this time since the study is no longer considered pivotal. This was discussed and agreed on in the filing meeting on 09/19/2013.

2.1.2 What are the proposed dosage(s) and route(s) of administration?

The proposed dose of PENNSAID 2% is 2 mL (2 pumps, 40 mg) on each painful knee, 2 times a day. The proposed route of administration is by the topical route only.

2.2 General Clinical Pharmacology

2.2.1 What is the pharmacokinetics of PENNSAID 2% formulation and its relative bioavailability compared to PENNSAID 1.5% formulation and oral diclofenac tablet?

The pharmacokinetic (PK) of PENNSAID 2% formulation was evaluated in three relative bioavailability studies (Study COV05100070, Study COV05100175 and Study MNK1530250). Two of them (Study COV05100070, Study COV05100175) were submitted in the original NDA 204623. Based on the OSI memo dated December 18, 2012, due to the lack of reserve samples, the authenticity of test and reference drug products administered can not be confirmed for both studies. Therefore, the data from these two studies can not be accepted for further Agency's review (see the original NDA review dated 01/28/13 in Darrrts and in Appendix of this review).

Study MNK15310250 is a randomized, open-label, multiple dose, two-way crossover study. The primary objective is to evaluate the PK, bioavailability and safety of diclofenac after PENNSAID 2% compared to PENNSAID 1.5%. Thirty-two subjects were enrolled and 30 subjects completed the study, 25 subjects were included in the PK analysis. All 32 subjects were included in the safety analysis. The study duration is approximately 12 weeks, consisting of a screening period and two treatment periods of 8 days separated by 15-day washout period. PENNSAID 2% (2 pumps (40 mg diclofenac sodium) per knee) was applied both knees BID for 7 days, PENNSAID 1.5% (40 drops (19.3 mg diclofenac sodium) per knee) was applied both knees QID for 7 days. The total daily dose of diclofenac was approximately 160 mg, and 154 mg for PENNSAID 2%, and PENNSAID 1.5%, respectively. On day 8, PENNSAID 2% (40 mg per knee) was only dosed once at time 0 hr, and PENNSAID 1.5% (19.3 mg per knee) was only dosed twice at time 0, and time 6 hr.

The mean diclofenac plasma profiles for PENNSAID 2% were summarized in Figures 2.1 and 2.2.

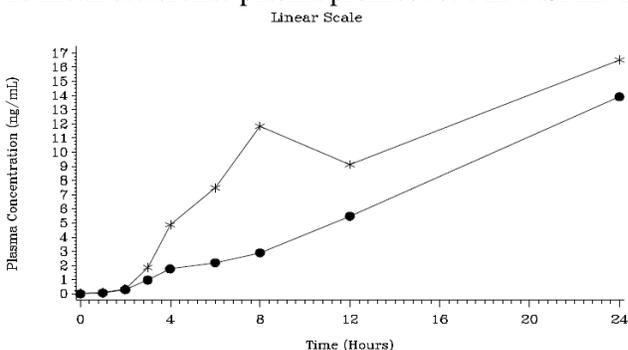


Figure 2.1 Mean plasma diclofenac concentrations for topical treatments from 0-24 hours (Day 1)

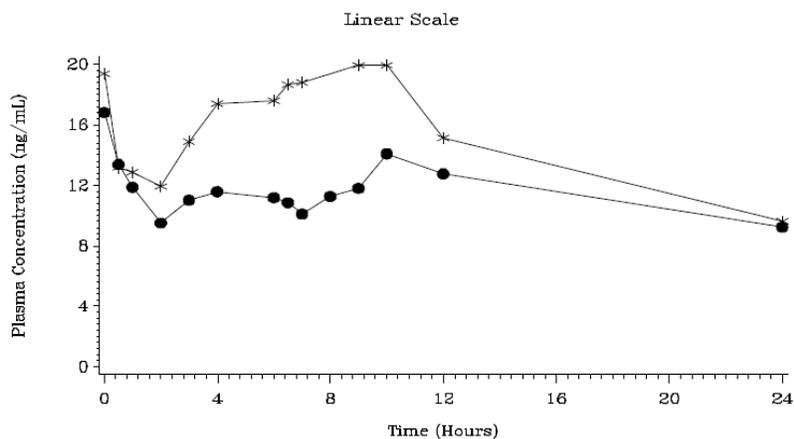


Figure 2.3 Mean plasma diclofenac concentrations for topical treatments from 169 to 192 hours (Day 8, 0 to 24 hours)

The PK parameters from this study were summarized in Table 2.1:

Table 2.1 Summary of Day 1 and Day 8 (Steady State) Diclofenac Pharmacokinetic Parameters for Study MNK15310250

	Study MNK15310250 (n=25)		Study COV05100070 (n=30) (OSI failed)	From NDA 20947 Review by Dr. David Lee
Parameters Mean (SD)	PENNSAID 2% Topical solution 40 mg/knee BID	PENNSAID 1.5% Topical solution 19.3 mg/knee QID	Diclofenac Sodium Tablet 75 mg BID	Diclofenac Sodium 50 mg Tablet (Single dose)
Day 1				
AUC ₀₋₁₂ (ng•h/mL)	77.27 (49.89)	27.46 (23.97)	(b) (4)	6300 (AUC _{0-inf})
C _{max} (ng/mL)	12.16 (7.66)	2.30 (2.02)		1500-1600
Day 8				
AUC ₀₋₁₂ ^{SS} (ng•h/mL)	204.58 (111.02)	141.49 (92.47)	(b) (4)	NA
C _{max} ^{SS} (ng/mL)	25.24 (12.95)	17.04 (11.28)		NA

NA: not available

Because the PENNSAID 2% formulation is intended for chronic use, it is more relevant to compare the systemic exposure at steady state. At steady state on Day 8, the systemic exposure for PENNSAID 2% formulation is higher than PENNSAID 1.5% formulation. The BE analysis result between PENNSAID 2% topical solution and PENNSAID 1.5% topical solution on Day 8 can be found in Table 1.2. The results show that the AUC₀₋₁₂ and C_{max} value from PENNSAID 2% topical solution at steady state was 49% and 46% higher compared to PENNSAID 1.5% topical solution, respectively.

Table 2.2 BE analysis results on Day 8 in Study MNK15310250

Parameter	PENNSAID 2%	PENNSAID 1.5%	Ratio, 90% CI
C _{max} ^{ss} (ng/mL)	25.24	17.04	145.68 (125.35-176.35)
AUC ₀₋₁₂ ^{ss} (ng h/mL)	204.58	141.49	149.162 (123.16-180.66)

For the comparison of PENNSAID 2% topical solution to the oral diclofenac sodium tablet, as the data from Study COV05100070 are considered unacceptable (OSI failed), systemic exposure of diclofenac following oral administration of a single dose of 50 mg diclofenac sodium was also obtained from NDA 20947 review by Dr. David Lee dated 7/1/2009 in Dartrts. Following oral administration of a single dose of 50 mg diclofenac sodium, the systemic exposure of diclofenac from NDA 20947 review were 6300 ng•h/mL for AUC_{0-inf} and 1500-1600 ng/mL for C_{max}. In Study COV05100070 which failed OSI inspection, diclofenac AUC₀₋₂₄ and C_{max} were (b) (4) ng•h/mL and (b) (4) ng/mL, respectively, following oral administration of 75 mg diclofenac sodium BID at Day 1. Based on the results from both studies, it is reasonable to conclude that the systemic exposure of diclofenac following PENNSAID 2% topical solution at the steady state on Day 8 will be much lower compared to that following oral diclofenac sodium tablet.

In conclusion, diclofenac AUC₀₋₁₂ and C_{max} value from PENNSAID 2% topical solution at steady state were 49% and 46% higher compared to those from PENNSAID 1.5% topical solution, respectively, at steady state on Day 8, and they are much lower compared to those from oral diclofenac tablet.

2.3 Analytical Section

What bioanalytical methods are used to assess concentrations?

(b) (4) Analytical Report Project RAHI2 described the validation study of the quantitative bioanalytical procedures used for the determination of Diclofenac in support of Study MNK15310250 in this NDA. All methods were validated with respect to sensitivity, accuracy, and precision. The summary of bio-analytical method and validation report can be found in Table 2.4.

Table 2.4 Summary of bio-analytical method and validation report

In-Trial Assay Performance for Diclofenac in Heparin Human Plasma

Parameter	QC Samples	Standard Curve Samples
Concentration (ng/mL)	0.300, 0.750, 3.00, 12.0, 75.0, and 11.9 ³	0.100, 0.200, 0.400, 1.60, 6.0, 25.0, 80.0, and 100
Interday Precision (% CV)	3.87 to 6.97	3.28 to 6.67
Interday Accuracy (%)	-5.37 to 6.78	-1.33 to 1.49
Correlation (Range of R ² values)	N/A	0.9946 to 0.9998
Linear Range (ng/mL)	N/A	0.100 to 100
Sensitivity/LLOQ (ng/mL)	N/A	0.100

3 PRELIMINARY LABELING RECOMMENDATIONS

Here are some high-level labeling comments. Line-by-line label edits will be done at a later date.

Presented below are preliminary labeling comments from the Clinical Pharmacology perspective. The *blue bolded italic* words indicate the addition text, and the ~~bold strike through~~ words indicate the deletion.

12.3 Pharmacokinetics:

Absorption:

After a ^(b) administration of PENNSAID ^(b) ₍₄₎ topical solution (40 mg/knee every 12 h; total daily diclofenac exposure: 80 mg/knee) for 7.5 days, *the mean (SD) AUC_{0-12} and mean (SD) C_{max} were 77.27 (49.89) ng•h/mL and 12.16 (7.66) ng/mL, respectively, on Day 1; and 204.58(111.02) ng•h/mL and 25.24 (12.95) ng/mL, respectively, at steady state on Day 8.* After administration of ^(b) ₍₄₎
~~to~~ PENNSAID 1.5% topical solution (19.3 mg/knee every 6 h; total daily diclofenac exposure 77.2 mg/knee), *the mean (SD) AUC_{0-12} and mean (SD) C_{max} were 27.46 (23.97) ng•h/mL and 2.30 (2.02) ng/mL, respectively, on Day 1; and 141.49 (92.47) ng•h/mL and 17.04 (11.28) ng/mL, respectively, at steady state on Day 8.* ^(b) ₍₄₎

(b) (4)

(b) (4)

The pharmacokinetics and effect of PENNSAID (b) (4) were not evaluated under the conditions of heat application, occlusive dressings overlay, or exercise following product application. Therefore, concurrent use of PENNSAID (b) (4) under these conditions is not recommended.

Distribution:

Diclofenac is more than 99% bound to human serum proteins, primarily to albumin.

Diclofenac diffuses into and out of the synovial fluid. Diffusion into the joint occurs when plasma levels are higher than those in the synovial fluid, after which the process reverses and synovial fluid levels are higher than plasma levels. It is not known whether diffusion into the joint plays a role in the effectiveness of diclofenac.

Metabolism:

Five diclofenac metabolites have been identified in human plasma and urine. The metabolites include 4'-hydroxy-, 5-hydroxy-, 3'-hydroxy-, 4',5-dihydroxy- and 3'-hydroxy-4'-methoxy diclofenac. The major diclofenac metabolite, 4'-hydroxy-diclofenac, has very weak pharmacologic activity. The formation of 4'-hydroxy diclofenac is primarily mediated by CYP2C9. Both diclofenac and its oxidative metabolites undergo glucuronidation or sulfation followed by biliary excretion. Acylglucuronidation mediated by UGT2B7 and oxidation mediated by CYP2C8 may also play a role in diclofenac metabolism. CYP3A4 is responsible for the formation of minor metabolites, 5-hydroxy and 3'-hydroxy-diclofenac.

Excretion:

Diclofenac is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites.

Little or no free unchanged diclofenac is excreted in the urine.

Special Populations:

Pediatric: The pharmacokinetics of PENNSAID (b) (4) has not been investigated in pediatric patients.

Race: Pharmacokinetic differences due to race have not been studied.

4 APPENDIX
4.1 Original NDA Review

CLINICAL PHARMACOLOGY REVIEW

NDA:	204623
Brand Name:	PENNSAID 2% (Proposed by the Sponsor)
Generic Name:	Diclofenac sodium topical solution 2%
Indication:	Treatment of (b) (4) osteoarthritis of the knee(s)
Dosage Form:	Solution
Strengths:	40. (b) (4) mg/2 mL
Route of Administration:	Topical
Dosing regimen:	2 mL (40. (b) (4) mg)/knee twice daily
Applicant:	Mallinckrodt Inc.
OCP Division:	DCP2
Clinical Division:	DAAAP (OND-170)
Submission Date:	May 4, 2012
Reviewers:	Ying Fan, Ph.D
Team Leader:	Yun Xu, Ph. D.

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EXECUTIVE SUMMARY

1.1 Recommendations

The Office of Clinical Pharmacology finds NDA 204623 not acceptable from a Clinical Pharmacology perspective due to the failed OSI inspection results on both Studies COV05100070 and COV05100175. The Sponsor will need to repeat the relative bioavailability study with PENNSAID 2%, PENNSAID 1.5%, and oral diclofenac tablet.

1.2 Phase IV commitments

None

1.3 Summary of Clinical Pharmacology findings

The sponsor is submitting a 505 (b)(2) new drug application for the PENNSAID (diclofenac sodium topical solution 2%) in a metered-dose pump indicated for treatment of [REDACTED]^{(b) (4)} of primary osteoarthritis of the knee(s). A product with lower strength, PENNSAID 1.5% formulation, was approved on November 4, 2009 [REDACTED]^{(b) (4)} under NDA 20947. The Sponsor claimed this new formulation was to improve the product's ease of use to optimize patient compliance and therefore enhance the public safety benefits of topical NSAID utilization. Based on the PENNSAID 1.5% formulation, PENNSAID 2% formulation was further developed to reduce the dosing frequency from 4 times daily (QID) to twice daily (BID) while retaining a similar total daily dose of diclofenac with comparable product performance.

This application was originally submitted as a supplement for the NDA 20947. It was considered as a new dosage form during the filing stage, therefore the Agency asked the sponsor to submit as a new NDA.

The Sponsor's clinical development program is comprised of 2 Phase 1 relative bioavailability studies (Study COV05100070 and Study COV05100175) and 1 clinical efficacy and safety study in patients with primary osteoarthritis of the knee with moderate flare after washout of stable pain therapy (Study COV05100031). This review will focus on Study COV05100070 and Study COV05100175.

Relative Bioavailability

The relative bioavailability of diclofenac was evaluated in two multiple dose PK studies, Study COV05100170 and Study COV05100175.

Study COV05100070 is a randomized, open-label, multiple-dose, 3-way crossover study. It compared PENNSAID 2% formulation BID (using the original container-closure system) with PENNSAID 1.5% formulation QID and oral diclofenac tablets BID after multiple doses. The oral comparator used in the relative bioavailability study COV05100070 was Sandoz oral diclofenac tablet (ANDA74394), which is a generic to VOLTAREN tablet (NDA19201). VOLTAREN tablet is no longer in the US market, and ANDA74394 is listed as a reference listed drug (RLD) in the Orange Book. After discussion within the team in the filing stage, it was decided that that Sponsor can use ANDA74394 as the comparator in the relative BA study, but they will need to use NDA19201 as the listed drug for the Agency's previous efficacy and safety findings for their 505(b)(2) application.

Study COV05100175 is randomized, open-label, multiple-dose, 2-way crossover study, comparing PENNSAID 2% topical solution (using to-be-marketed container-closure system) and PENNSAID 1.5% topical solution.

OSI inspection findings

OSI inspection was requested on both Studies COV05100170 and COV05100175. Based on the OSI memo dated December 18, 2012, due to the lack of reserve samples, the authenticity of the test and reference drug products administered cannot be confirmed for both studies. Therefore, data cannot be accepted for further Agency's review. The Sponsor will need to repeat the relative BA study with PENNSAID 2%, PENNSAID 1.5%, and oral diclofenac tablet.

2 QUESTION BASED REVIEW

2.1 General Attributes/Background

2.1.1 What is the pertinent regulatory background of PENNSAID 2%?

The current submission is a 505 (b)(2) new drug application for the PENNSAID (diclofenac sodium topical solution 2%) in a metered-dose pump indicated for treatment of (b) (4) (b) (4) osteoarthritis of the knee(s). A lower strength of PENNSAID, 1.5%, was approved on November 4, 2009 (b) (4). This new formulation, PENNSAID 2%, was intended to improve the product's ease of use to optimize patient compliance and therefore enhance the public safety benefits of topical NSAID utilization. Based on the PENNSAID 1.5% formulation, PENNSAID 2% formulation was further developed to reduce the dosing frequency from 4 times daily (QID) to twice daily (BID) while retaining a similar total daily dose of diclofenac with comparable product performance.

This application was originally submitted as a CMC supplement for the NDA 20947 (PENNSAID 1.5%). It was considered as new dosage form in the filing stage, therefore the sponsor was asked to submit the application as a new NDA.

At the EOP2 meeting, the Division indicated that the sponsor needs to conduct a 12-week clinical efficacy and safety study for the proposed PENNSAID 2% formulation. However, the Sponsor conducted a 4-week study instead when the NDA was submitted. The sponsor used the OGD Draft Guidance on Diclofenac Sodium for PENNSAID 1.5% (NDA 20947) to support their position. The Sponsor indicated "Upon review of the guidance, Mallinckrodt feels that the study design reflects the Sponsor's understanding of FDA's intent for comparability and in vivo bioequivalence. In agreement with the clinical objectives outlined in the guidance, COV05100031 evaluated the primary endpoint in patients with osteoarthritis of the knee after 4 weeks of treatment. The study demonstrated that PENNSAID 2% was efficacious and well tolerated."

According to the OGD Draft Guidance, two *in vivo* studies are recommended: a single-dose, two-way crossover pharmacokinetics study in healthy subjects to demonstrate bioequivalence on systemic exposure between the innovator and the generic, and a 4-week randomized, double blind, parallel, placebo-controlled clinical trial in osteoarthritis patients to demonstrate bioequivalence on clinical efficacy endpoints. At the filing meeting, the Division decided to consider the sponsor's rationale during the review process. In addition, the Division thought the PK data may be sufficient to support approval, based on the fact that PENNSAID 2% showed a comparable systemic exposure compared to PENNSAID 1.5%. Therefore, the relative bioavailability study between the PENNSAID 2% and PENNSAID 1.5% could be considered pivotal; OSI inspection was requested on both Studies COV05100170 and COV05100175. During the review process, the Division has determined that the efficacy will mainly be supported by a 4-week efficacy study and the PK study result will just be supportive.

2.1.2 What are the proposed dosage(s) and route(s) of administration?

The proposed dose of PENNSAID 2% is 2 mL (2 pumps, 40 (b) (4) mg) on each painful knee, 2 times a day. The proposed route of administration is by the topical route only.

2.1.3 Was the final to-be-marketed product used in the clinical development program?

The final to-be-marketed container-closure system was only used in the relative bioavailability study COV05100175. It was not used in the relative bioavailability study COV05100170 and the clinical efficacy study COV05100031; an “original” closure system was used. An IR was sent to the Sponsor by CMC to clarify the difference between the two systems. According to the sponsor, the delivery pump was different between the two systems. In the response to the CMC IR, the sponsor indicated that the dispensing weight per actuation using the original container-closure system and the final to-be-marketed container-closure system was different. The dispensing weight per actuation using the original container-closure system (b) (4) was (b) (4) g higher than the final to-be-marketed container-closure system (~1.0 g). Due to failed OSI inspection, results from both Studies COV05100070 and COV05100175 are not acceptable. The Sponsor will need to repeat the relative bioavailability study with PENNSAID 2%, PENNSAID 1.5%, and oral diclofenac tablet.

The final to-be-marketed container-closure was also not used in clinical efficacy study COV05100031. The clinical review team is aware of this and we will decide whether it is acceptable.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology studies and clinical studies used to support dosing or claims?

This submission includes three clinical trials, including 1 safety and efficacy trial, and 2 bioavailability and pharmacokinetics (PK) trials:

- **COV05100170:** Phase 1, R, OL, MD, 3-way cross over, PK, bioavailability, safety, 7.5 days, 21 days washout
 - PENNSAID 2% formulation, 2 mL 40 (b) (4) mg/knee BID (use original container-closure system, every 12 hr day 1-7 (time 0, 12 hr), one dose on day 8 (time 0 hr))
 - PENNSAID 1.5% formulation, 1.2 mL 19.3 mg/knee QID (every 6 hr day 1-7, one dose on day 8 (time 0 hr))
 - Oral diclofenac (Sandoz, ANDA 74394) delayed-release tablets 75 mg BID (every 12 hr day 1-7 (time 0, 12 hr), one dose on day 8 (time 0 hr))
- **COV05100175:** Phase 1, OL, MD, 2-way cross over, PK, bioavailability, safety
 - PENNSAID 2% formulation, 2 mL 40 (b) (4) mg/knee BID (use to-be-marketed container-closure system, every 12 hr day 1-7, one dose on day 8 (time 0 hr))
 - PENNSAID 1.5% formulation, 1.2 mL 19.3 mg/knee QID (every 6 hr day 1-7, two doses on day 8 (time 0, 6 hr))
- **COV05100031:** Phase 2, R, DB, parallel group, 4-week, efficacy, safety
 - PENNSAID 2% formulation 2mL BID for 4 weeks (use original container-closure system)
 - Control (vehicle)

2.2.2 What is previously known about the pharmacokinetics of diclofenac?

The following is the PK information from approved PENNSAID 1.5% label:

Absorption:

Diclofenac systemic exposure from PENNSAID application (4 times daily for 1 week) was approximately 1/3 of the diclofenac systemic exposure from the Solaraze (diclofenac topical gel) application (twice daily for 4 weeks).

Distribution:

Diclofenac is more than 99% bound to human serum proteins, primarily to albumin. Diclofenac diffuses into and out of the synovial fluid. Diffusion into the joint occurs when plasma levels are higher than those in the synovial fluid, after which the process reverses and synovial fluid levels are higher than plasma levels. It is not known whether diffusion into the joint plays a role in the effectiveness of diclofenac.

Metabolism:

Five diclofenac metabolites have been identified in human plasma and urine. The metabolites include 4'-hydroxy-, 5-hydroxy-, 3'-hydroxy-, 4',5-dihydroxy- and 3'-hydroxy-4'-methoxy diclofenac. The major diclofenac metabolite, 4'-hydroxy-diclofenac, has very weak pharmacologic activity. The formation of 4'-hydroxy diclofenac is primarily mediated by CPY2C9. Both diclofenac and its oxidative metabolites undergo glucuronidation or sulfation followed by biliary excretion. Acylglucuronidation mediated by UGT2B7 and oxidation mediated by CPY2C8 may also play a role in diclofenac metabolism. CYP3A4 is responsible for the formation of minor metabolites, 5-hydroxy and 3'-hydroxydiclofenac

Elimination:

Diclofenac is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites. Little or no free unchanged diclofenac is excreted in the urine.

2.2.3 What is the pharmacokinetics of PENNSAID 2% formulation and its relative bioavailability compared to PENNSAID 1.5% formulation and oral diclofenac tablet?

The pharmacokinetic (PK) of PENNSAID 2% formulation was evaluated in two relative bioavailability studies (Study COV05100070 and Study COV05100175). Since OSI recommends that data from both studies cannot be accepted for further agency's review, the study results will not be discussed in this review.

Study COV05100070 is a randomized, open-label, multiple-dose, 3-way crossover study. The primary objective is to evaluate the pharmacokinetics and bioavailability of diclofenac after topical application of PENNSAID 2% compared to PENNSAID 1.5% and oral administration of Sandoz 75 mg oral diclofenac sodium delayed-release tablets. Thirty healthy subjects were involved in the study and were randomly assigned to 1 of the 6 treatment sequences. Each study treatment was separated by a 21 day washout period. PENNSAID 2% (40 ^(b)₍₄₎ mg (2 mL) per knee) was applied BID for 7 days. PENNSAID 1.5% (40 drops (1.2 mL, 19.3 mg) per knee) was applied QID for 7 days. Sandoz 75 mg diclofenac oral tablet was administered orally BID for 7 days. On day 8, PENNSAID 2% (40 ^(b)₍₄₎ mg per knee), PENNSAID 1.5% (19.3 mg per knee) and Sandoz (75 mg) were only dosed once at time 0 hr.

Study COV05100175 is a randomized, open-label, multiple dose, two-way crossover study. The primary objective is to evaluate the pharmacokinetics and bioavailability of diclofenac after PENNSAID 2% compared to PENNSAID 1.5%. Thirty-two healthy subjects were enrolled and 29 subjects completed the study. The study duration is approximately 9 weeks, consisting of a screening period and two 7.5-day treatment periods separated by a 21-day washout period. PENNSAID 2% (2 mL (40 ^(b)₍₄₎ mg) per knee) was applied both knees BID for 7 days. PENNSAID 1.5% (1.2 mL (19.3 mg) per knee) was applied both knees QID for 7 days. On day 8, PENNSAID 2% (40 ^(b)₍₄₎ mg per knee) was only dosed once at time 0 hr, and PENNSAID 1.5% (19.3 mg per knee) was only dosed twice at time 0, and time 6 hr.

2.2.4 Effect of heat application, occlusive dressings overlay, or exercise

The pharmacokinetics and effect of the product were not evaluated under the conditions of heat application, occlusive dressings overlay, or exercise following product application. Therefore, concurrent use under these conditions is not recommended.

2.3 OSI inspection results

OSI inspection was requested on both Studies COV05100170 and COV05100175. Based on the OSI memo dated December 18, 2012 in Darrrts, it was noted that following the inspections of the analytical and clinical portions of studies COV05100070 and COV05100175, OSI reviewers found no objectionable conditions were observed for the analytical portions of the studies. However, for the clinical portions of the studies, due to the lack of reserve samples, the authenticity of the test and reference drug products administered cannot be confirmed. Therefore, data cannot be accepted for further Agency's review.

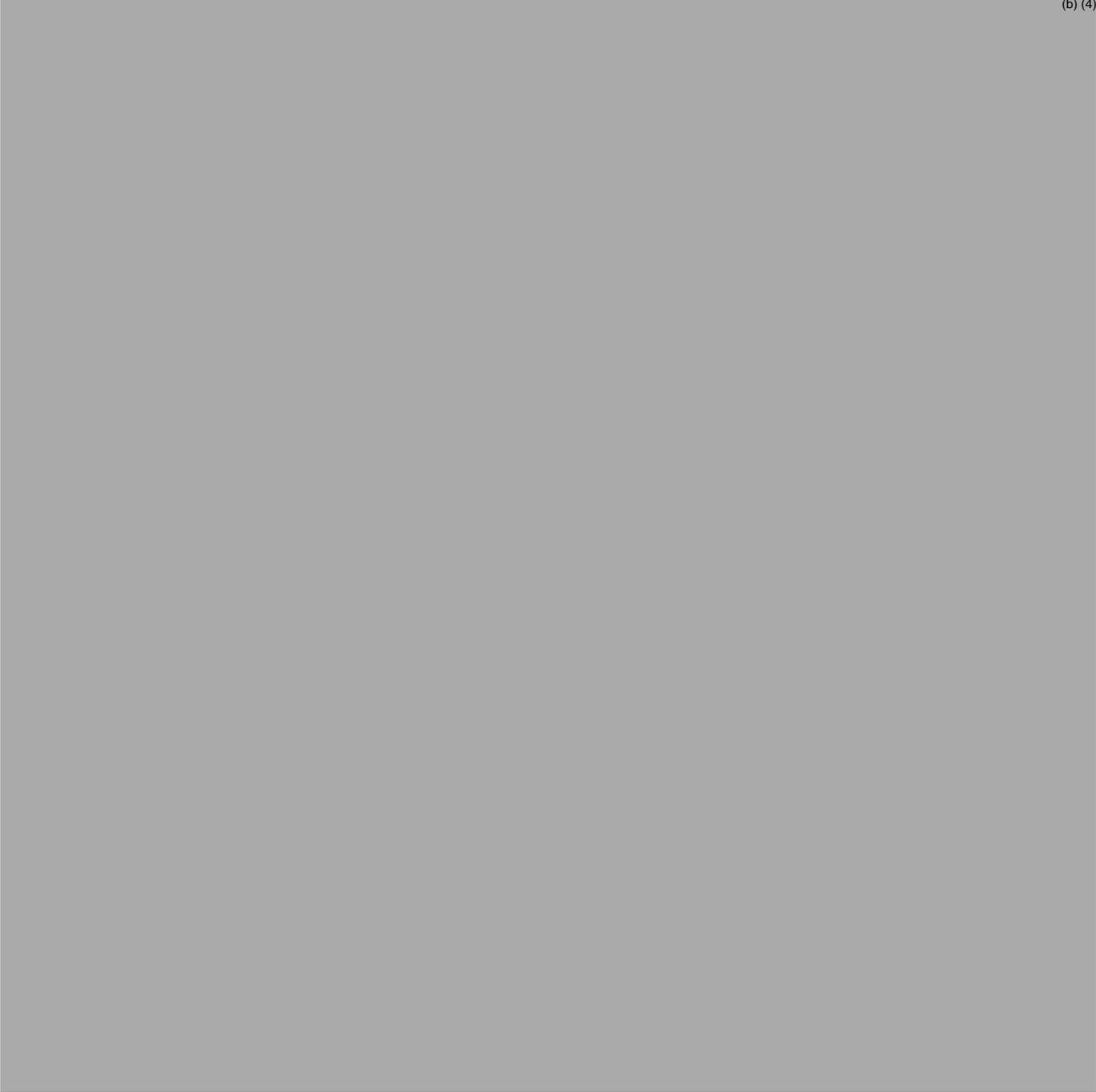
Based on the Division's current position, studies COV05100070 and COV05100175 are no longer considered pivotal (see 2.1.1 regulatory background). In this setting we would not have requested an inspection of these studies, but now that we already have the information. After extensive discussion within the review team, with regulatory expert for 505(b)(2) application, and with higher management, it was decided the study results can not be used to support the application. Therefore, the Sponsor will need to repeat the relative BA study with PENNSAID 2%, PENNSAID 1.5%, and oral diclofenac tablet.

3 PRELIMINARY LABELING RECOMMENDATIONS

Presented below are preliminary labeling comments from the Clinical Pharmacology perspective. The *blue italic* words indicate the addition text, and the ~~strike-through~~ word indicates the deletion. Since OSI recommends data from both studies COV05100070 and COV05100175 cannot be accepted for further Agency's review, results from these two studies cannot be included in the label.

12.3 Pharmacokinetics

(b) (4)



The pharmacokinetics and effect of (b) (4) were not evaluated under the conditions of heat application, occlusive dressings overlay, or exercise following product application. Therefore, concurrent use of (b) (4) under these conditions is not recommended.

Distribution:

Diclofenac is more than 99% bound to human serum proteins, primarily to albumin.

Diclofenac diffuses into and out of the synovial fluid. Diffusion into the joint occurs when plasma levels are higher than those in the synovial fluid, after which the process reverses and synovial fluid levels are higher than plasma levels. It is not known whether diffusion into the joint plays a role in the effectiveness of diclofenac.

(b) (4)

Metabolism:

Five diclofenac metabolites have been identified in human plasma and urine. The metabolites include 4'-hydroxy-, 5-hydroxy-, 3'-hydroxy-, 4',5-dihydroxy- and 3'-hydroxy-4'-methoxy diclofenac. The major diclofenac metabolite, 4'-hydroxy-diclofenac, has very weak pharmacologic activity. The formation of 4'-hydroxy diclofenac is primarily mediated by CYP2C9. Both diclofenac and its oxidative metabolites undergo glucuronidation or sulfation followed by biliary excretion. Acylglucuronidation mediated by UGT2B7 and oxidation mediated by CYP2C8 may also play a role in diclofenac metabolism. CYP3A4 is responsible for the formation of minor metabolites, 5-hydroxy and 3'-hydroxy-diclofenac.

Excretion:

Diclofenac is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites.

Little or no free unchanged diclofenac is excreted in the urine.

Special Populations:

Pediatric: The pharmacokinetics of PENNSAID (b) (4) has not been investigated in pediatric patients.

Race: Pharmacokinetic differences due to race have not been studied.

4 APPENDIX

4.1 OSI inspection form

11 Page(s) have been Withheld in Full immediately following this page. These pages are included in the Other Review Section. See document dated 12/19/2012.

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/s/

YUN XU

01/28/2013

Dr. Ying Fan is on extended medical leave so I finalized and Darrrts the review.

ADDENDUM TO CLINICAL PHARMACOLOGY REVIEW

NDA:	204623
Brand Name:	PENNSAID 2% (Proposed by the Sponsor)
Generic Name:	Diclofenac sodium topical solution 2%
Indication:	Treatment of (b) (4) osteoarthritis of the knee(s)
Dosage Form:	Solution
Strengths:	40 (b) (4) mg/2 mL
Route of Administration:	Topical
Dosing regimen:	2 mL (40 (b) (4) mg)/knee twice daily
Applicant:	Mallinckrodt Inc.
OCP Division:	DCP2
Clinical Division:	DAAAP (OND-170)
Submission Date:	May 4, 2012
Reviewers:	Ying Fan, Ph.D
Team Leader:	Yun Xu, Ph. D.

Summary

This is an addendum to the clinical pharmacology review in Dartrts on 01/28/2013. In the original review, the recommendation is “The Office of Clinical Pharmacology finds NDA 204623 not acceptable from a Clinical Pharmacology perspective due to the failed OSI inspection results on both Studies COV05100070 and COV05100175. The Sponsor will need to repeat the relative bioavailability study with PENNSAID 2%, PENNSAID 1.5%, and oral diclofenac tablet.” In this addendum, the last sentence in the recommendation will be amended to “The Sponsor will need to repeat the relative bioavailability study with PENNSAID 2% and PENNSAID 1.5%”.

Discussion

In the End of Phase 2 meeting minutes on 09/25/2006 for the corresponding IND 75045, the Sponsor was told that “if the Sponsor is thinking of referencing Voltaren®, Solaraze®, and PENNSAID® 1.5% solution, the Sponsor should consider a three reference-arm study approach comparing Voltaren®/Solaraze®/ PENNSAID® 1.5% solution to PENNSAID® Gel.”. In the post-meeting comments, the Sponsor was told that “if you plan on relying on the Agency’s finding of safety for Solaraze®, a relative bioavailability study should be completed in order to establish the relevance of the dermal carcinogenicity data to your product and accurately describe the exposure margins for your product label.”

When the sponsor submitted this NDA, relative bioavailability study between the proposed PENNSAID 2% formulation, already approved PENNSAID® 1.5% formulation, and oral diclofenac tablet was conducted. (Note: Since oral Voltaren tablet is discontinued from the US market, a generic product was used in the study.) The review team determined that since the Sponsor is relying on Solaraze for the preclinical data on photosensitivity, dermal carcinogenicity, and photocarcinogenicity, Solaraze does not need to be included in the relative bioavailability study because the data relied upon is from topical exposure and a biobridge is not necessary for this type of reliance. However, the completed relative bioavailability failed OSI inspection so the data cannot be accepted for further Agency’s review.

Therefore, the Sponsor was asked to repeat the relative bioavailability study with PENNSAID 2%, PENNSAID 1.5%, and oral diclofenac tablet in the clinical pharmacology review in darrrts on 01/28/2013.

This submission was further discussed in the 505(b)(2) clearance committee in Mid February, 2013. Based on email discussion with Ms. Sara Stradley, Acting Associate Director for Regulatory Affairs Office of Drug Evaluation II, the committee decided that the relative bioavailability study with oral Voltaren tablet is not needed from a regulatory perspective since the original PENNSAID 1.5% NDA referenced the oral Voltaren tablet in the 505(b)(2) application, and the current NDA is cross-referencing PENNSAID 1.5%. Therefore, the Sponsor will only need to repeat the relative bioavailability study with proposed PENNSAID 2% and already approved PENNSAID 1.5%.

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