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APPLICATION NUMBER:

204623Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, M.D.
Subject	Deputy Division Director Summary Review
NDA/BLA #	204623
Applicant Name	Mallinckrodt, Inc.
Date of Submission	August 7, 2013
PDUFA Goal Date	February 7, 2014
Proprietary Name / Established (USAN) Name	PENNSAID/ Diclofenac Sodium Topical Solution, 2% w/w
Dosage Forms / Strength	Topical Solution, 2%
Proposed Indication(s)	1. For the (b) (4) (b) (4) of osteoarthritis of the knee
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	N/A
Statistical Review	N/A
Pharmacology Toxicology Review	N/A
CMC Review/OBP Review	NA
Clinical Pharmacology Review	Ying Fan, Ph.D., Yun Xu, Ph.D.
OSI	Jyoti B. Patel, Ph.D., Sam H. Haidar, R.Ph., Ph.D.
CDTL Review	Ellen Fields, M.D., MPH
OSE/DMEPA	Vicky Borders-Hemphill, Pharm.D., Jamie Wilkins Parker, Pharm.D, Morgan Walker, Pharm.D.
OPDP//DAPR I	Eunice Chung-Davies, Pharm.D.
OMP/DMPP	Nathan Caulk, MS, BSN, RN, Barbara Fuller, RN, MSN, CWOCN, LaShawn Griffins, MSHS-PH, BSN, RN

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication ErrorsPrevention
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OPDP=Office of Prescription Drug Promotion
DAPR I = Division of Advertising and Promotional Review I
DCDP=Division of Consumer Drug Promotion
OMP=Office of Medical Policy Initiatives
DMPP=Division of Medical Policy Programs

Signatory Authority Review Template

1. Introduction

This NDA represents a new formulation of topical diclofenac sodium and cross references Pennsaid, a topical solution of diclofenac sodium, 1.5%, approved on November 4, 2009. The original formulation of Pennsaid is dosed as 40 drops applied to the knee four times daily. The formulation under review is more concentrated, 2%, more viscous than the original Pennsaid formulation, and is intended to be dosed twice daily with administration via a metered-dose pump. (b) (4) As discussed below, the findings of the clinical efficacy study (b) (4) are sufficient to support an indication for the treatment of the pain of osteoarthritis of the knee.

Initially submitted as an efficacy supplement, the application was changed to a new NDA as the product is a new formulation. The application is a 505(b)(2) and relies on the Agency's prior findings for Pennsaid, a 505(b)(2) application which relied on prior findings for Solaraze and oral Voltaren. The first cycle received a complete response action as a result of the findings of the Office of Scientific Investigation, that the clinical samples were not retained at the clinical site where the relative bioavailability studies were conducted so that the authenticity of the test and reference drug products administered could be confirmed. There was evidence of efficacy for diclofenac topical solution 2%, for the management of the pain of osteoarthritis in a 4-week adequate and well controlled clinical study based on the WOMAC Pain subscale. (b) (4) No new safety concerns were identified in the clinical program. A repeat relative bioavailability study comparing diclofenac topical solution 2% with Pennsaid was required to respond to this deficiency and the results of such a study have been submitted by the Applicant.

2. Background

Diclofenac is nonsteroidal anti-inflammatory drug currently approved in oral and topical formulations including a topical solution, topical gel and patch, and as an ophthalmic solution.

From my original memo:

> The Applicant formulated the product under review, diclofenac topical solution 2%, with a different strength and a different dosing regimen than Pennsaid. As a result, the Applicant was advised that one adequate and well-controlled 12-week study was required to support a finding of efficacy, in addition to the relative bioavailability data required for a 505(b)(2) application. This advice was provided at an End-of-Phase 2 meeting in 2006 and at a guidance meeting in 2008. However, the only clinical efficacy study submitted in this NDA was a 4-week efficacy study originally intended to be an exploratory study. The Applicant presented an argument that the study was consistent with the study design described in the

Office of Generic Drug's (OGD) *Draft Guidance on[Topical] Diclofenac Sodium*. The Guidance outlines that the clinical development approach for generic topical diclofenac products should consist of one bioequivalence (BE) study and one BE study with a clinical endpoint. The latter study design is a comparison of a generic diclofenac sodium topical gel, the reference listed drug, or placebo for the treatment of patients with osteoarthritis for 4 weeks. The Applicant's rationale was that diclofenac sodium topical solution 2% had similar diclofenac systemic exposure to Pennsaid and so, this guidance should apply. While this argument was initially considered inadequate, it was thought that if the pharmacokinetic data were the same, additional efficacy may not be necessary and, so, the application was filed. After reconsideration, the Applicant's argument that the studies required under the draft guidance were sufficient to support the application was found acceptable. As the exposure from the two products appeared to be similar, it was decided that there was no need to hold this application to a substantially higher burden of evidence.

3. CMC/Device

No new CMC information was submitted in this complete response.

Diclofenac sodium topical solution 2% w/w is proposed for twice daily administration provided in a metered-dose container. As described during the first review cycle, the DMF for the drug substance, and the data supporting the drug product and metered dose pump container/closure system were adequate.

I concur with the conclusions reached by the chemistry reviewer during the first review cycle regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months. There are no outstanding CMC issues to preclude approval.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical information was submitted in support of the complete response and there were no deficiencies from the first cycle that required additional nonclinical data to address. The Applicant had cross-referenced all of the nonclinical pharmacology and pharmacokinetic literature previously submitted to NDA 20947, Pennsaid 1.5% and had conducted a series of new nonclinical pharmacokinetic studies were submitted that compared the absorption and distribution of diclofenac to the knees of swine after single and repeated administrations of PENNSAID 2% vs. the marketed PENNSAID 1.5% product. Extraction studies were conducted to determine the safety of the container/closure system. With the exception of (b) (4) all of the compounds extracted were below the qualification threshold of 5 mcg/day. Adequate safety justification was provided for the (b) (4)

I concur with the conclusions reached by the pharmacology/toxicology reviewer during the original review cycle that there are no outstanding pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

As noted in my original review:

> The basis for approving diclofenac sodium topical solution 2% relies in part on the prior findings for Pennsaid. A relative bioavailability study comparing the two products is necessary to form not only a scientific bridge for relying on the Agency's prior findings, but to determine the systemic exposure to diclofenac for both products. While these products are intended to act locally, the relative systemic exposure can provide important information about the ability of the diclofenac to penetrate from topical administration. This is based on the reasoning that if the same amount can penetrate into the blood, the same amount reaches local tissues. Initially, as no 12-week efficacy study was submitted, consideration was given to relying primarily on the pharmacokinetic data to support the application. As a result, the two relative bioavailability studies, Study COV05100070 and Study COV05100175, were initially considered pivotal studies in supporting the application and were submitted for inspection by the Office of Scientific Investigation (OSI). The OSI inspection found that reserve samples were not retained at the clinical study site and, therefore, the authenticity of the test and reference drug products administered cannot be confirmed for either study. As a result, OSI concluded that the data cannot be accepted for Agency's review and the Applicant must repeat the relative BA study with Pennsaid 1.5%.
>
> As detailed in Dr. Fan's review, Study COV05100170 was a Phase 1, randomized, open-label, multiple-dose, 3-way crossover study. Diclofenac sodium topical solution 2%, 2 mL 40.4 mg/knee twice daily (original container-closure system), Pennsaid 1.5%, 1.2 mL 19.3 mg/knee four times daily and oral diclofenac (Sandoz, ANDA 74394) delayed-release tablets 75 mg twice daily were administered for 7 days with one dose on Day 8 (one dose on Day 8 for Pennsaid.)
>
> Study COV05100175 was a Phase 1, randomized, open-label, multiple-dose, 2-way crossover study. Diclofenac sodium topical solution 2%, 2 mL, 40.4 mg/knee, twice daily (to-be-marketed container-closure system) and Pennsaid 1.5% 1.2 mL, 19.3 mg/knee, four times daily were administered for 7 days with one dose on Day 8 (two doses on Day 8 for Pennsaid.)
>
> The steady state AUC and Cmax were similar for both topical diclofenac products and considerably lower than the oral product. Details of the results are not included based on the OSI recommendations.

The Applicant submitted a new relative bioavailability study, MNK15310250, a randomized, open-label, multiple-dose, two-way crossover study comparing Pennsaid 2% and Pennsaid 1.5% that was reviewed by Dr. Fan. As noted in Dr. Fan's review:

> 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 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 DARRTS. 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} 1271.10 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 AUC_{0-12} 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.

During the first review cycle, it was determined that, as Pennsaid (NDA 20947) referenced the Agency's prior findings for oral Voltaren tablet and Solaraze to support systemic safety and efficacy, and dermal safety and carcinogenicity, respectively, cross reference to Pennsaid and a relative bioavailability study with Pennsaid are sufficient to support reliance of these findings for diclofenac sodium topical solution 2%. I concur with the conclusions reached by the clinical pharmacology reviewer that the new relative bioavailability study provides an adequate scientific bridge, in conjunction with known exposure to oral diclofenac from NDA 20-947, for the Applicant to rely on the Agency's prior findings of safety and efficacy.

There are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

No new clinical efficacy studies were submitted in response to the CR action. The single four-week efficacy study conducted with this product was reviewed during the first cycle and details of the study can be found in the first cycle reviews. The study did demonstrate a finding of efficacy for pain associated with OA of the knee, (b) (4) .

As noted in my first cycle review:

> This 4-week efficacy study will be suitable to support efficacy as part of a weight of evidence argument, in conjunction with pharmacokinetic data once the relative bioavailability study is repeated. As long as the exposure to diclofenac is similar for the 1.5% and 2% diclofenac topical products in the repeat study, together with the results of Study COV05100031, there will be adequate evidence to support a finding of efficacy.

There are no outstanding issues concerning efficacy that preclude approval for an indication of the pain of OA.

8. Safety

During the first review cycle, the safety of diclofenac sodium topical solution 2% was reviewed by Dr. Spaulding who found no new or unexpected findings. As noted in my first cycle review:

> The safety database consists of 189 subjects and the Applicant is also relying on the safety of Pennsaid given the similarity of the products. As noted in Dr. Fields' review:
>
> > The safety profile of diclofenac sodium topical solution 2% was assessed in 130 patients with primary OA of the knee, and 59 subjects in Phase 1 studies. Of the 130 subjects with OA, 129 received an average of 28 days of study drug BID on the study knee. Eighty-one subjects received an average of 28 days of BID treatment on the contralateral knee.
>
> Dr. Spaulding reported that no serious adverse events or deaths were reported in the safety population. Early discontinuations were few, and discontinuations due to adverse events were predominantly local application site reactions. Approximately 40% of patients in both treatment groups had treatment emergent adverse events, the most common of the relevant events were application site dryness, application site exfoliation, and application site erythema.

There were an additional 32 healthy volunteers exposed to a eight days of dosing of Pennsaid 2% and eight days of dosing of Pennsaid 1.5% during the new relative bioavailability study, MNK15310250 which included assessment of vital signs, laboratory data, skin irritation assessments, and recording of treatment emergent adverse events (TEAE). All 32 subjects were included in the safety analysis. There were no deaths or serious adverse events. Two subjects discontinued from the study early, one due to mild flu-like symptoms occurring 11 days after the last dose of period 1. The second subject was discontinued by the investigator who discovered that the subject misrepresented their identity. Overall, 21 subjects (66%) reported at least 1 TEAE after treatment with Pennsaid 2% compared to 14 subjects *47%) following treatment with Pennsaid 1.5%. The most comment TEAE was application site dryness, followed by application site pruritus, application site pain, application site exfoliation, application site erythema, application site rash and excoriation are presented in Table 1. All resolved by study end. The occurrence of excoriation was commented on further by the Applicant, noting that the verbatim terms were abrasions and scratches on the lower extremities. The following application site reaction TEAEs occurred in only one subject were: application site discomfort (Pennsaid 2% only), application site irritation (Pennsaid 1.5% only), and application site papules (Pennsaid 1.5% only).

Table 1: Summary of TEAEs Experienced by at Least 5% of Subjects[a] (All Dosed Subjects)

Preferred Term	PENNSAID 2% N = 32 n (%)	PENNSAID 1.5% N = 30 n (%)
Application Site Dryness	12 (37.5)	6 (20.0)
Application Site Pain	4 (12.5)	1 (3.3)
Application Site Pruritus	5 (15.6)	1 (3.3)

Application Site Exfoliation	1 (3.1)	3 (10.0)
Application Site Erythema	2 (6.3)	0
Application Site Rash	2 (6.3)	0
Nasopharyngitis	2 (6.3)	0
Excoriation	3 (9.4)	0

a Occurring in 2 or more subjects.
Note: A treatment-emergent AE (TEAE) is defined as an event that emerges during treatment having been absent pre-treatment, or worsens relative to the pre-treatment state.
At each level of subject summarization, a subject is counted once if the subject reported 1 or more events.
Percentages are based on the number of subjects who received the specified treatment.
Adverse events were coded by system organ class and preferred term using MedDRA version 16.0.
Source: Sponsor Table 12.2.2-1, Table 14.3.1-1 and Appendix 16, Listing 16.2.7-1.

Skin irritation was assessed and found to be similar to Pennsaid 1.5%. Systemic adverse events were reported in single patients only, most in either Pennsaid 2% or Pennsaid 1.5% and were unlikely treatment-related except for possible abdominal pain (Pennsaid 1.5%). There were no clinically notable changes in laboratory data, ECGs, or vital signs.

None of the adverse events reported were novel or unexpected for this topical product.

9. Advisory Committee Meeting

No advisory committee meeting was held for this reformulation of an existing product with no new safety concerns.

10. Pediatrics

Pediatric studies under PREA for the entire age range of birth to <17 years were waived because the studies would be highly impracticable to conduct, since the number of pediatric patients with OA is too small to study. The Pediatric Research Committee (PeRC) agreed to this waiver on January 30, 2013.

11. Other Relevant Regulatory Issues

There are no unresolved relevant regulatory issues.

12. Labeling

Several proposed proprietary names such as (b) (4) were submitted prior to the proposed name, Pennsaid, and were either withdrawn voluntarily by the Applicant or found unacceptable by DMEPA. The name, Pennsaid, was found acceptable.

Suggested edits for improving the package insert, medication guide, and the carton and container labels have been received from DMEPA, DMPP and DCDP and have been implemented.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – Approval

- Risk Benefit Assessment

The Applicant has adequately addressed the deficiency from the first cycle by submitting a new relative bioavailability study demonstrating the pharmacokinetic properties of Pennsaid 2% and Pennsaid 1.5% and creating the scientific bridge for relying on prior findings for Pennsaid 1.5%. The results of the relative bioavailability study demonstrating greater exposure for Pennsaid 2% and the four-week efficacy study confirming efficacy are sufficient to support a finding of efficacy. The safety profile is consistent with Pennsaid 1.5% and, apart from local application site reactions, consistent with the relatively low systemic absorption of diclofenac. The cutoff point for diclofenac exposure for which there are no longer risks for systemic toxicity is unknown. The relationship of low dose aspirin used for cardioprophylaxis, 81 mg, and adverse events including risk for gastrointestinal bleeding is well known, even though this is substantially lower than the dose used for analgesia and to treat rheumatologic conditions (325 to 650 mg every 4 to 6 hours as needed, not to exceed 4000 mg per day). Therefore, in the absence of data to the contrary, even the topical diclofenac products, including Pennsaid, with relatively low systemic exposure to diclofenac compared to oral products, will be labeled with the full NSAID class warnings and have the NSAID class medication guide.

While there was evidence of efficacy for diclofenac topical solution 2%, for the management of the pain of osteoarthritis in a 4-week adequate and well-controlled clinical study based on the WOMAC Pain subscale, (b) (4)

- Recommendation for Postmarketing Risk Management Activities

None

- Recommendation for other Postmarketing Study Commitments

None

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/s/

SHARON H HERTZ
01/16/2014