CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-122

SUMMARY REVIEW

Summary Basis for Regulatory Action

Date	October 17, 2007
From	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia and Rheumatology Products
Subject	Division Director Summary Review
NDA #	22-122
Proprietary / Established (USAN) Names	Voltaren® Gel (diclofenac sodium topical gel)
Dosage Forms / Strength	gel, 1%
Proposed Indication(s)	for the relief of the pain of osteoarthritis of joints amenable to topical treatment, such as the knees or those of the hands
Action:	*Approval*

1. Introduction to Review

Voltaren® Gel is a topical formulation of the NSAID diclofenac. There are multiple oral formulations of diclofenac. Other approved products containing diclofenac include an ophthalmic solution, a patch for the treatment of pain associated with minor strains, sprains and contusions, and a gel indicated for the treatment of actinic keratosis. Voltaren® Gel will be the first topical NSAID approved under an NDA in the U.S. for the treatment of the pain of osteoarthritis.

Review of the CMC portion of this application was completed by Sue-Ching Lin, M.S., R.Ph. Review of the pharmacology and toxicology data was completed by L. Steve Leshin, DVM, Ph.D. and a secondary review of the toxicology findings was completed by Adam Wasserman, Ph.D. Review of the clinical pharmacology and biopharmaceutics data was completed by David Lee, Ph.D. A statistical review was completed by Ruthanna Davi, M.S. A clinical review was completed by Neville Gibbs, M.D. Mwango Kashoki, M.D. provided a secondary review of the application as clinical team leader for this project. Consultation on this application was also obtained from the Division of

Dermatologic and Dental Products (DDDP), the Division of Drug Marketing, Advertising and Communications (DDMAC), the Division of Medication Errors and Technical Support (DMETS), the Division of Surveillance, Research and Communication Support (DSRCS), the Division of Scientific Investigations (DSI), and the Study Endpoints and Labeling Development team (SEALD).

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

Novartis initially requested an [redacted] indication for the [redacted]. At a pre-IND meeting with the Division of Analgesic, Anti-Inflammatory and Ophthalmologic Drug Products (DAAODP) and [redacted] in February of 2003, the sponsor was advised that the product would not be appropriate for [redacted]. They were further advised to develop the product as a prescription product for the treatment of OA. The sponsor was also asked to develop the product for the indication of the [redacted] in efficacy trials performed to support that indication.

In May of 2005 DAAODP was merged with the Division of Anesthetics, Critical Care and Addiction Drug Products to form the Division of Anesthesia, Analgesia and Rheumatology Products (DAARP). During the review of this application, the clinical and statistical review teams determined that one of the two pivotal trials in support of efficacy, Study VOSG-PE-315 (Study 315), did not achieve a statistically significant treatment effect on the global outcome measure. Technically, according to the study's pre-specified statistical analysis plan and the initial requirements for demonstration of efficacy, this would mean that the application could not support approval for the indication. However, both of the pivotal studies achieved statistically significant treatment effects for the pain endpoints. Over the past two years, DAARP has considered the indication of "[redacted]", and an indication of "the treatment of pain" which only requires a demonstration of efficacy on a pain outcome measure. The studies of Voltaren® Gel support efficacy in that the product is able to reduce pain, but given that it was only studied in patients with OA of the hands and knees, it cannot be assumed that it is suitable for [redacted]. Given the advice provided to the sponsor by DAAODP to only study patients with OA, and given the efficacy results, the indication that best reflects what is known about this product is "the treatment of the pain of OA in joints amenable to topical treatment." In a recent teleconference with the sponsor they agreed to this new indication.

Further discussion of the trial results can be found below in the Clinical/Statistical Section; and Dr. Kashoki's review provides a detailed description of the regulatory history of this application.

3. CMC/Microbiology/Device

There were no notable issues raised by the CMC reviewers.

4. Nonclinical Pharmacology/Toxicology

This product contains a novel excipient, cocoyl caprylocaprate, an [redacted], at a level of [redacted]. It is described as carpylic (decanoic)/capric (octanoic) acid esters of saturated fatty alcohols C_{12-18}, derived from [redacted] while the standard FDA policy would require full toxicologic evaluation of a novel excipient commensurate with its duration of use prior to product approval, Drs. Leshin and Wasserman have determined that local tolerance has been adequately addressed through its inclusion in the product formulation used in clinical studies and that a post-marketing evaluation of dermal carcinogenicity and reproductive toxicity may be undertaken in this case for the following reasons:

1. The excipient is derived from [redacted] and presents no obvious safety concern based on structural similarity to other known compounds approved for use in topical products.
2. [redacted] the excipient would be expected to be largely retained on the skin surface with little or no systemic absorption. Other types of excipients, such as penetration enhancers, may present additional risk due to direct absorption, as well as promotion of increased absorption of other inactive ingredients.
3. No safety signals were seen in the clinical studies. In addition, there have been no signals related to Voltaren® Emulgel, which has 20 years of foreign marketing experience, and cocoyl caprylocaprate is a component of numerous cosmetics and sunscreens marketed in the U.S.

Although there would normally be an additional requirement for an evaluation of genotoxicity, any concerns regarding carcinogenicity will be addressed through the conduct of the dermal carcinogenicity evaluation and, therefore, genotoxicity studies will not be requested as a post-marketing commitment.

The review team initially requested that the sponsor provide demonstration of an equivalent degradation profile between their product and their reference listed product, Solaraze™, to address the photo-degradant profiles prior to approval. However, they concluded that this information may be submitted as a post-marketing commitment as dermal carcinogenicity has already been appropriately referenced, and any photo-carcinogenicity evaluation can be averted with appropriate labeling to avoid or minimize

sun exposure. The referenced Solaraze™ photo-carcinogenicity study did demonstrate apparent promotion of dermatologic cancers. However, this study was limited in drug exposure due to tolerability issues and a better study with Voltaren® Gel is not likely to be feasible. While I agree with Drs. Leshin and Wasserman that the label should caution against sun exposure, in reality, it is unlikely that most patients who use this product on their hands will be able to avoid frequent sun exposure and, thus, the label must acknowledge the risks of photo-induced carcinogenicity. In any case, it is important that, as information from the Solaraze™ photocarcinogenicity study is being referenced as a basis for labeling comments, the sponsor should provide a toxicological risk assessment of photo-degradants which are considered unique or are found at substantially greater levels when compared against those in the referenced product. It is acceptable for this information to be provided as a post-marketing commitment.

5. Clinical Pharmacology/Biopharmaceutics

5.1. As described in Dr. Lee's review and summarized in Dr. Kashoki's review, the sponsor performed clinical pharmacology studies with Voltaren® Gel that demonstrated that systemic exposure to diclofenac is, on average, 17 times lower than that seen with oral diclofenac administration, when the gel is used according to the labeled recommendations. With maximal use (both hands, both knees QID), the systemic exposure is approximately 20% of what is seen with an oral dose of diclofenac of 50 mg TID. The C_{max} with maximal exposure is 2% that of an oral dose of diclofenac.

5.2. Drug-drug interactions

There are no concerns regarding drug-drug interactions due to the low levels of systemic exposure with this product.

5.3. Pathway of Elimination

Again, there are no concerns due to the low systemic levels.

5.4. Demographic interactions/special populations

There are no concerns related to demographic interactions or special populations.

5.5. Thorough QT study or other QT assessment

No QT studies or assessments are necessary for this well-known moiety.

5.6. Notable issues

No increase in absorption or systemic exposure was found in a study of the effects of heat applied to one knee after application of Voltaren® Gel.

6. Clinical Microbiology

There are no microbiological concerns with this topical formulation. It is not to be used on non-intact skin.

7. Clinical/Statistical

7.1. General Discussion

As noted above in Section 2, due to the results of the primary outcome analyses, the Division reached agreement with the sponsor on a different endpoint than that originally agreed upon and submitted in the application. The addition of the phrase, "...of joints amenable to topical treatment, such as the hands and knees" to the indication was based on extensive internal discussion as well as discussion with the sponsor during the course of the review. Agreement was reached that this language would more clearly address for prescribers any concerns regarding which joints should be targeted for treatment with this product.

No new significant safety concerns specific to this product were found in the clinical database, with mild, reversible skin reactions seen as the most common adverse events.

7.2. Efficacy

7.2.1. Dose identification/selection and limitations

Dose selection was appropriate.

7.2.2. Phase 3/essential clinical studies, including design, analytic features, and results

See the primary and secondary clinical and statistical reviews for the details of the pivotal efficacy trials. The most salient findings of these studies was the fact that the "Knee" study, Study VOSG-PN-310 (Study 310), demonstrated a statistically significant treatment effect on each of the three primary outcome measures, while the "Hand" study, Study 315, did not show a statistically significant treatment for the global measure. Tables 1, and 3a/3b from Dr. Kashoki's review (pages 12 and 15-16, respectively) summarize these data, including sensitivity analyses with

varying degrees of conservative imputation methodology, and have been reproduced below:

Table 1: Primary Efficacy Results – Study VOSG-PN-310 – Knee OA

Primary Efficacy Analysis (Modified Efficacy Subpopulation*)				
Endpoint	**DSG**	**Placebo**	**LS mean difference (Placebo-DSG)**	**p-value**
WOMAC pain (0-20)	5.9	7.3	1.3	0.02
WOMAC function	20.2	25.9	5.7	0.003
Global rating of disease	34.1	42.6	8.5	0.02
Analysis using BOCF imputation				
WOMAC pain	6.4	7.9	1.5	0.02
WOMAC function	21.2	27.4	6.2	0.001
Global rating of disease	35.4	44.1	8.6	0.02
Analysis using "mean of the same group" imputation				
WOMAC pain	5.5	5.9	0.5	0.37
WOMAC function	18.8	22.2	3.4	0.04
Global rating of disease	30.2	35.7	5.6	0.07
Analysis using "mean of the other group" imputation				
WOMAC pain	5.6	5.6	0.0	>0.99
WOMAC function	19.4	20.9	1.5	0.37
Global rating of disease	31.2	33.5	2.3	0.46

* Excludes all subjects whose pain on movement score in the target knee declined between the screening visit and baseline visit or with a score of >1 on the abridged pain index for the contralateral knee at the baseline visit.

Table 3a: Week 4 Efficacy Results (FDA analysis) – Study VOSG-PN-315 – Hand OA

Primary Efficacy Analysis (modified ITT population)**				
Endpoint	**DSG N=198**	**Placebo N=187**	**LS mean difference (Placebo-DSG)**	**p-value**
WOMAC pain (0-100)	42.6	49.7	6.9	0.011
AUSCAN total	43.7	50.2	6.3	0.011
AUSCAN function*	44.7	50.8	6.6	0.010
Global rating of disease	37.5	41.9	4.9	0.08

* Applicant's analysis, dominant hand only. (Source: Applicant's Study Report for VOSG-PE-315 and Appendix 5, Section 5.1.2)

** Excludes subjects with baseline scores less than 10 for each primary endpoint.

Table 3b: Week 4 Sensitivity Analysis Results (Applicant's Analysis) – Study VOSG-PN-315 – Hand OA

Sensitivity Analysis (modified ITT population*)				
Endpoint	**DSG N=198**	**Placebo N=187**	**LS mean difference (Placebo-DSG)**	**p-value**
Analysis using BOCF imputation				
WOMAC pain	44.3	49.7	5.5	0.03
AUSCAN total	45.2	50.6	5.4	0.03
Global rating of disease	39.3	43.8	4.5	0.08
Analysis using "mean of the same group" imputation				
WOMAC pain	41.6	46.4	4.8	0.048
AUSCAN total	43.2	47.6	4.4	0.06
Global rating of disease	37.2	40.8	3.6	0.14
Analysis using "mean of the other group" imputation				
WOMAC pain	42.1	46.0	3.9	0.11
AUSCAN total	43.5	47.3	3.8	0.11
Global rating of disease	37.5	40.5	3.0	0.23

Source: Applicant's Study Report for VOSG-PE-315 and Appendix 5, Section 5.1.2
* Excludes subjects with baseline scores less than 10 for each primary endpoint.

It is worth noting that the BOCF imputation methodology is appropriately conservative in these studies, while the additional imputation strategies employed are inappropriately onerous.

7.2.3. Other efficacy studies

It is of note that there were two earlier studies, one each in hand and knee, that were unsuccessful in demonstrating any statistically significant treatment effects.

7.2.4. Discussion of primary and secondary reviewers' comments and conclusions

Drs. Gibbs and Kashoki concluded that the results of the "Hand" trial, Study 115, were compelling enough, and supported by additional secondary endpoints and analyses, to demonstrate efficacy for the indication of [redacted]. I am unable to agree with this conclusion. The prespecified statistical analysis plan for this study clearly required that statistically significant treatment effects be demonstrated on each of the three primary outcome measures at Week 4. This was not the case for the global measure. Although this measure did show a statistically significant treatment effect at Week 6, I do not agree with Dr. Kashoki that this is likely due to the

need for more prolonged exposure to the product before efficacy can be achieved. Indeed, I would suspect that, if efficacy had not been demonstrated after a few days, the product would be unlikely to work later. It may simply be that the waxing and waning nature of OA pain allowed demonstration on one day and not on another. In any case, I cannot change the efficacy standards for this product to allow a conclusion that they have two adequate and well-controlled trials demonstrating statistically significant treatment effects per the prespecified analysis plan.

However, as I noted in the introduction above, it is possible to conclude that they have demonstrated replicated efficacy for the treatment of pain, particularly since that is what they initially planned to study, and they only took on the more complicated outcome measure at DAAODP's request. They have submitted compelling evidence in both Studies 310 and 315 that their product provides some effect in the treatment of the pain of OA in the hands and knees. These "superficial" joints are logically more amenable to treatment with a topical product. The product was not studied for and is unlikely to be effective for OA pain in deeper joints, and the safety of this product has not been established for use on the back or neck.

7.2.5. Pediatric use/PREA waivers/deferrals

Under PREA, we have waived the requirement for pediatric studies of OA as this condition occurs only in extremely rare cases in children.

7.2.6. Notable issues

[See above]

7.3. Safety

7.3.1. General safety considerations

There were no unexpected adverse events or unusual incidences of the events expected for diclofenac in the clinical studies. The most common events were mild, reversible dermatologic reactions.

As systemic exposure was demonstrated, albeit quite low, the NSAID template labeling for safety was incorporated into the product's package insert.

8. Advisory Committee Meeting

An advisory committee was not determined to be necessary for this low systemic exposure topical NSAID gel with a benign safety profile and a standard efficacy evaluation.

9. Other Regulatory Issues

There are no other regulatory issues or concerns.

10. Financial Disclosure

[See primary clinical review]

11. Labeling

A standard NSAID MedGuide has been incorporated into the product label as for all NSAID products with any systemic exposure. This MedGuide, however, also incorporates language specific to the special dosing and administration concerns for this product.

12. DSI Audits

[See primary clinical review]

13. Conclusions and Recommendations

13.1. Regulatory action

Approval

13.2. Safety concerns to be followed postmarketing

There are no unusual concerns for this product other than skin reactions which appear to be mild and reversible. We will, of course, monitor for any evidence of typical NSAID-related cardiovascular, gastrointestinal or other adverse events in the postmarketing population.

13.3. Risk Minimization Action Plan

A Risk Minimization Action Plan is not necessary for this product.

13.4. Postmarketing studies

13.4.1. Required studies

There are no required studies under PREA as OA is extremely rare in pediatric patients.

13.4.2. Commitments (PMCs)

1. Provide a study to evaluate the photo-contact allergic potential of Voltaren® Gel.

Protocol Submission:	by March 31, 2008
Study Start:	by June 30, 2008
Final Report Submission:	by December 31, 2009

2. Provide a rationale to support the safe use of the novel excipient cocoyl caprylocaprate that would preclude the submission of preclinical studies.

Rationale submission:	by January 31, 2008

If the proposed rationale is determined to be inadequate, the following studies will be required:

a. A dermal carcinogenicity evaluation of cocoyl caprylocaprate in two species. One of these studies may be conducted in a transgenic mouse model upon concurrence from the Agency.

Protocol Submission:	by July 31, 2008
Study Start:	by April 30, 2009
Final Report Submission:	by April 30, 2012

b. A full reproductive toxicology evaluation of cocoyl caprylocaprate consistent with ICH-S5A unless the topical route can be demonstrated to produce non-detectable systemic exposure to the excipient.

Protocol Submission:	by April 30, 2008
Study Start:	by June 30, 2008
Final Report Submission:	by June 30, 2009

3. Provide a toxicological risk assessment of photo-degradants which are considered unique or are found at substantially greater levels when compared against a characterization of photo-degradants in the referenced drug Solaraze™.

Protocol Submission:	by June 30, 2008
Study Start:	by August 31, 2008
Final Report Submission:	by December 31, 2008

13.4.3. Other agreements

None

13.5. Comments to be conveyed to the applicant

None

APPEARS THIS WAY
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/s/

Bob Rappaport
10/17/2007 07:20:55 PM
MEDICAL OFFICER