CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-304

SUMMARY REVIEW

11/20/08

Summary Basis for Regulatory Action

Date	November 20, 2008
From	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # Supp #	N[ ]
Applicant Name	Johnson & Johnson Pharmaceutical Research & Development
Proprietary / Established (USAN) Names	TBD Tapentadol
Dosage Forms / Strength	Tablet 50 mg, 75 mg, 100 mg
Proposed Indication(s)	1. Relief of moderate to severe acute pain
Action:	*Approval*

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1. Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding tapentadol and the reader should refer to the reviews in the action package for a more detailed discussion. Tapentadol is a mu opioid agonist and also has norepinephrine reuptake inhibitor activity. Tapentadol is structurally related to tramadol and has similar pharmacological actions, however tapentadol has demonstrated abuse liability similar to hydromorphone. This will require scheduling for tapentadol (schedule II) unlike tramadol which is not scheduled.

As detailed in Drs. Shibuya, Fields, Rappaport and Norton's reviews, tapentadol has demonstrated efficacy in replicated adequate clinical trials. The safety profile appears typical for an opioid agent and also similar to tramadol in certain aspects. As such, if agreements can be made regarding labeling, I will recommend an approval action.

Efficacy

This has been thoroughly covered in Drs. Shibuya, Fields and Norton's reviews and I will not elaborate on their reviews. The evaluation for efficacy was demonstrated in two studies, 32 and 33. Study 32 was conducted in bunionectomy subjects evaluated with a Summed Pain Intensity Difference over 48 hours (SPID48). This study demonstrated clear efficacy, dose response and was supported by secondary endpoints.

Study 33 was conducted in subjects with degenerative joint disease of the hip or knee with efficacy evaluated by a SPID-5 days. Efficacy was again demonstrated and supported by secondary endpoints, although there was not demonstration of a dose response.

Safety

The safety profile for tapentadol is similar to other opioids and to tramadol. The most common AEs as stated in Dr. Shibuya's review are those typical of an opioid and were nausea, dizziness, vomiting, somnolence, constipation and pruritus.

There are other safety concerns to be considered and the product should have labeling to reflect these concerns and uncertainties. Seizures were observed in rats at high doses and in dogs at clinically relevant doses. During clinical trials, there was one case in which a Phase 1 study participant had a seizure, but this was confounded as discussed in Dr. Shibuya's review. I note that subjects at risk for seizures were excluded from the trials and labeling should reflect this concern and uncertainty regarding how subjects at risk may react if given tapentadol.

Another safety concern is in regard to the norepinephrine reuptake activity of this NME as this activity poses a concern of possible serotonin syndrome if used concomitantly with MAOIs, SSRIs etc. I also note that drug combinations which may pose an interaction problem were prohibited in the clinical trials and this should also be reflected in labeling.

Finally, abuse liability studies demonstrated liability similar to hydromorphone. This has sparked interest in requiring a medication guide. This probably has merit as it should be instructed that, even though this is similar to tramadol, it has much greater abuse liability issues.

Conclusions and Recommendations

Tapentadol has demonstrated efficacy for the relief of moderate to severe pain. It also has a safety profile that has both the characteristics of a typical opioid and tramadol. Tapentadol has the risks briefly outlined above, and labeling should reflect these concerns. Tapentadol was not taken to an Advisory Committee meeting as there are several previously approved agents in the opioid class of drugs and evaluation of the safety data did not reveal particular safety issues unexpected for this class or of tramadol-like agents. Additionally, design and results of the efficacy trials did not pose particular concerns. I agree that a medication guide is probably appropriate for tapentadol.

I believe, that with proper labeling, the risk: benefit considerations of tapentadol would allow marketing. As such, I recommend an Approval action if proper labeling can be negotiated with the sponsor.

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/s/

Curtis Rosebraugh
11/20/2008 04:20:21 PM
MEDICAL OFFICER

11/16/08

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS

Summary Review for Regulatory Action

Date	November 16, 2008
From	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia and Rheumatology Products
Subject	Division Director Summary Review
NDA#	22-304
Applicant Name	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Date of Submission	January 22, 2008
PDUFA Goal Date	November 23, 2008
Proprietary Name / Established (USAN) Name	N/A Tapentadol hydrochloride
Dosage Forms / Strength	Immediate-release tablets, 50 mg, 75 mg and 100 mg
Proposed Indication	For the relief of moderate to severe acute pain
Recommended Action:	Approval

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