# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**022328Orig1s000**

# OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022328

COMPLETE RESPONSE

Transcept Pharmaceuticals, Inc.
1003 W. Cutting Blvd., Suite 110
Pt. Richmond, CA 94804

Attention: Sharon Sakai, Ph.D.
Vice President, Regulatory Affairs

Dear Dr. Sakai:

Please refer to your September 30, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Intermezzo (zolpidem tartrate) 1.75 mg and 3.5 mg sublingual lozenge (sl).

We acknowledge receipt of your amendments dated:

| | | |
|---|---|---|
| January 14, 2011 | March 1, 2011 | March 8, 2011 |
| March 14, 2011 | March 29, 2011 | April 5, 2011 (2 submissions) |
| May 26, 2011 | June 3, 2011 | |

The January 14, 2011, submission constituted a complete response to our October 28, 2009, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

In our Complete Response to the original NDA submission, we agreed that efficacy had been adequately demonstrated for Intermezzo. However, we found that you had not presented adequate evidence about the safety of residual morning levels of zolpidem from Intermezzo, particularly if patients inadvertently re-dosed Intermezzo in a single night, or inadvertently dosed with less than 4 hours of bedtime remaining. Both of these risks appeared potentially to be increased compared to other zolpidem products by the middle-of-the-night (MOTN)-dosing of Intermezzo.

We indicated in our Complete Response that it appeared necessary for you to demonstrate both that (a) Intermezzo, when taken as directed, did not unacceptably impair next-morning driving ability, and that (b) dosing errors could be adequately minimized, or that the potential adverse effects of such dosing errors on driving safety could be shown to be acceptable.

We also stated in the CR letter that alternative packaging might help minimize the risk of dosing errors.

At the End-of-Review Meeting on January 20, 2010, you proposed alternative individual-dose packaging of Intermezzo that, on face, appeared to decrease concerns about risk of inadvertent re-dosing of Intermezzo. After full review of your current Complete Response, we agree that you have adequately mitigated this risk.

We remained concerned at the End-of Review Meeting that the alternative packaging you proposed might not adequately address the risk of impaired next-day driving from inadvertent dosing with less than 4 hours of bedtime remaining. We proposed that you might study the risk of dosing errors in a patient-use study prior to approval. However, you proposed conducting a study only of patient understanding of dosing instructions, arguing that a study that attempted to directly observe if patients actually followed dosing instructions would be neither possible nor useful, because patient behavior in the study would not be generalizable to actual clinical use. We agreed to consider your argument in your Complete Response.

After full review of your Complete Response, we agree with you that packaging and instructions clearly communicate that intermezzo must not be used with less than 4 hours of bedtime remaining. Importantly, however, we believe that this conclusion is consistent with the position that Intermezzo must still be shown to be safe in the context of ordinary, unavoidable deviations from labeled use. We agree with you that accurate measurement of such deviations is difficult because, for example, patients are more likely to dose correctly when under observation. We are still not convinced that a study of patient use is without value, as a high level of dosing errors would clearly be informative, but we would not compel you to conduct such a study. Instead, based in part on the deviations from dosing instructions that appear to have occurred in the outpatient efficacy study (ZI-12) despite the highly controlled study conditions, we conclude that it is likely that some proportion of patients will take Intermezzo with less than 4 hours of bedtime remaining. Although it is difficult to know how much patients will deviate from the 4 hour limit, it seems reasonable to consider that driving about 3 to 3.5 hours after dosing of Intermezzo should be considered as part of the safety review of Intermezzo.

During our review of your resubmission, we became concerned that patients at the high end of zolpidem exposure from Intermezzo would be at unacceptable risk of next-day impairment. We therefore asked you to conduct additional pharmacokinetic and pharmacodynamic analyses, which you submitted on May 26, 2011 (Amendment 40). In one analysis, you identified subjects in each PK study that were in the highest 10th percentile for exposure (based on Cmax, AUC, and zolpidem blood level at 4 hours post-dosing). Out of 25 subjects you identified, at 4 hours after Intermezzo 3.5 mg, 16 had a blood level above 40 ng/ml, 7 had a level above 60 ng/ml, and one had a blood level of ≈ 80 ng/ml. Several types of evidence from your development program suggest that such levels are likely to result in clinically important driving impairment. Zolpidem blood levels in the driving study (ZI-18) were not measured, but zolpidem blood levels from the PK studies suggest that the average zolpidem level in the 3-hour arm of the driving study was unlikely to be greater than ≈30- to 40 ng/ml. The 3-hour arm was positive in the symmetry analysis up to and including the 4 cm SDLP threshold, suggesting clinically meaningful impairment of driving in this range of zolpidem blood levels. It might be hypothesized that the

impaired subjects in the driving study at 3 hours were those who had above-average blood levels (i.e. blood levels > 40- or even 50 ng/ml) but even if the signal for impairment was driven largely by patients with such levels, as noted above, such levels commonly occur 4 hours after Intermezzo dosing. Of course, plasma zolpidem levels in such patients 3 to 3.5 hours after dosing would be even greater.

Additional concern arises from the fact that patients at the high end of the distribution have blood levels about the same as what was likely the average Cmax from Intermezzo 3.5 mg in the efficacy studies (PK was not measured in the efficacy studies). This blood level was, of course, shown to decrease MOTN sleep latency, and there is concern that a similar effect in the morning would increase the risk of falling asleep while driving. Moreover, these blood levels are double or more the likely average Cmax from 1.75 mg Intermezzo, a dose also that showed a statistically significant decrease in sleep latency (study ZI-06-010). Our concern about morning levels of zolpidem increasing the risk of falling asleep while driving is supported by the fact that such an event occurred in the driving study. It is also clear that women have, on average, greater zolpidem plasma levels at a given dose than men; estimates range from about 40-70% greater.

In your Complete Response, particularly your May 26, 2011 amendment, you argued that the morning blood levels described above do not impair driving. You base this conclusion largely on the fact that there was little correlation between zolpidem blood levels and some of the pharmacodynamic responses you measured, such as Digit Symbol Substitution Test (DSST). However, as we stated in our Complete Response to your original submission, we do not believe that measures such as DSST or patient questionnaires adequately address possible adverse effects of zolpidem on driving ability. In contrast, while the driving study did not examine different doses of Intermezzo, and acute tolerance could have affected pharmacodynamic response in relationship to time from dosing, the results suggest that higher blood levels of zolpidem (at earlier time points) are positively correlated with greater impairment of driving. More fundamentally, dose-response studies of zolpidem, including your inpatient efficacy study (ZI-06-010), appear to leave little doubt that pharmacodynamic response to zolpidem increases with dose in the range in question.

In your Complete Response, you provide a number of additional arguments in support of the safety of Intermezzo. However, we similarly do not find these arguments compelling.

You argue that Intermezzo is safer than other FDA-approved drugs for insomnia. Such arguments are fundamentally problematic in terms of both evidence and regulatory requirements; there appears to be no actual data supporting your claims, and evidence you present raising concern that other FDA-approved sleep drugs may be impairing does not diminish the regulatory requirement to demonstrate that Intermezzo is adequately safe. That said, we have considered your argument that the safety of currently approved drugs, including risk from misuse, can help in understanding the acceptability of risk from a new drug.

You assert that next-day impairment from Intermezzo will be much less than the risk from off-label, MOTN use of drugs approved for before-bed use. However, your conclusions are based on selective premises. For example, the potential for off-label use of Intermezzo is not acknowledged, and it is far from clear that off-label use of Intermezzo will be any less frequent,

or of less serious consequence, than off-label use of insomnia drugs intended for before-bed use. Similarly, your conclusions do not fully consider, or propose how to address, the fact that off-label MOTN use of some insomnia drugs (e.g. zaleplon) might be safer than off-label, or potentially even as-labeled use of Intermezzo.

Another comparative safety argument you present is based on *average* blood levels in the morning after use of various zolpidem products. You assert that residual levels from Intermezzo are no higher than residual levels from currently approved products. Your argument, however, does not consider the *range* of morning blood levels from these products; as discussed above, patients at the high end of exposure from Intermezzo are of particular safety concern. Also, your argument is based on cross-study comparisons, which are generally unreliable, particularly in the case of zolpidem, given the high degree of variability seen across PK studies.

For the above reasons, therefore, we can not conclude that you have adequately demonstrated that Intermezzo is safe.

We believe that a necessary first step in addressing our concerns about residual morning levels of zolpidem from Intermezzo would be a more thorough characterization of the distribution of blood levels that can occur the morning after dosing. While you have conducted a number of pharmacokinetic studies, we are concerned that the subjects in these studies may have been too homogenous to fully represent blood levels in the broader U.S. population. For example, while we acknowledge that the effect of race on zolpidem blood levels is not well-characterized, at least one published report suggests that race has a relatively large effect on zolpidem blood levels (Salva, P. and Costa, J., Clin Pharmacokinet 29, 1995). It is also not clear to us that the effect of body weight/composition on zolpidem pharmacokinetics has been adequately characterized.

While we do not exclude the possibility that you could present convincing evidence that the zolpidem blood levels from Intermezzo are safe, we would recommend as a second step that you pursue strategies to decrease morning zolpidem levels from Intermezzo, particularly levels at the high end of the distribution (e.g. through modification of dose, time, patient selection, etc.).

Finally, depending on the residual zolpidem levels that might result after mitigation strategies are implemented, it might be necessary for you to demonstrate, in an adequately powered study with demonstrated assay sensitivity, that the levels still present do not present an unacceptable risk of next-day impairment. This might be accomplished with a study generally similar to your current driving study, although we would be open to proposals for other types of studies.

## LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also

request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

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

If you have any questions, call Cathleen Michaloski, BSN, MPH, Sr. Regulatory Project Manager, at (301) 796-1123.

Sincerely,

*{See appended electronic signature page}*

Russell G. Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

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/s/

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CATHLEEN B MICHALOSKI
07/14/2011

RUSSELL G KATZ
07/14/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA #22328 **COMPLETE RESPONSE**

Transcept Pharmaceuticals, Inc.
1003 W. Cutting Blvd., Suite 110
Pt. Richmond, CA 94804

Attention: Sharon Sakai, Ph.D.
Associate Director, Regulatory Affairs

Dear Dr. Sakai:

Please refer to your September 30, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Intermezzo (zolpidem tartrate) 1.75 mg and 3.5 mg sublingual lozenge (sl).

We acknowledge receipt of your amendments dated:

| | | |
|---|---|---|
| December 16, 2008 | December 24, 2008 | January 12, 2009 |
| February 6, 2009 | March 5, 2009 | March 6, 2009 |
| March 12, 2009 | March 17, 2009 | March 19, 2009 |
| April 9, 2009 | April 16, 2009 | May 21, 2009 |
| May 22, 2009 | May 29, 2009 | June 4, 2009 |
| July, 1, 2009 | July 8, 2009 | July 10, 2009 |
| July 23, 2009 | July 30, 2009 | September 17, 2009 |

We have completed the review of your application, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

## CLINICAL

We believe that you have submitted substantial evidence of effectiveness for Intermezzo in the as-needed treatment of insomnia characterized by difficulty returning to sleep after middle-of-the-night (MOTN) awakening. However, we do not believe that you have adequately demonstrated that Intermezzo can reliably be used safely.

Intermezzo is intended as an as-needed treatment for difficulty returning to sleep after MOTN awakening, a unique insomnia indication for which safety has never before been established for any drug. As you acknowledge in your submission, key to any safe use of MOTN insomnia

treatment is adequate assurance that blood/tissue concentrations after final awakening do not result in residual effects. We do not find that such assurance has been provided.

First, we note that morning blood levels of zolpidem 4 hours after Intermezzo dosing would still be about 25 ng/mL. We agree that neither the Digit Symbol Substitution Test (DSST), a commonly used measure of pharmacodynamic effect of sedative-hypnotics, nor patient questionnaires, indicated residual pharmacodynamic effect from this blood level. However, we do not believe that these measures adequately address possible adverse effects from these zolpidem levels on driving ability. Such effects, if present, would seemingly present a clear safety risk.

In our review of the published literature on zolpidem and driving, we identified studies that increased our concern that residual blood levels from Intermezzo could present a safety risk from driving. In particular, Leufkens et al[1] recently reported that 5- to 6 hours after MOTN dosing of 10 mg zolpidem driving performance was 'moderately impaired.' While zolpidem blood levels were apparently not measured in that study, data from the Intermezzo development program suggest that zolpidem blood levels 6 hours after dosing 10 mg of zolpidem would be about 24 ng/mL. Of concern, the average zolpidem blood level 4 hours after dosing of Intermezzo 3.5 mg is, as noted above, about 25 ng/mL, essentially identical to levels reported to be associated with impaired driving. Thus, from the safety data you provided, the division can not conclude that even when used as directed, Intermezzo is adequately free of next-day adverse effects on driving. In addition, as you know from our communications during the NDA review period and as discussed below, the division has been concerned that patients will not, in fact, be able to consistently use Intermezzo according to labeling, thereby potentially greatly increasing the risk posed by residual zolpidem levels.

The division requested a teleconference, held with you 22 April 2009, to discuss our concerns that the following types of medication errors might be associated with use of Intermezzo:

- Inadvertent dosing with less than 4 hours of bedtime remaining
- Inadvertent redosing in a single night

These concerns arise not only because of the inherent pharmacology of the drug, but also in part because of the nature of the proposed use. That is, in our view, intentional dosing in the middle of the night predisposes to increased errors of the types described above, because patients know that this treatment is to be taken when they awake in the middle of the night.

Our concern about these two types of dosing errors is supported by findings in Study ZI-12, the 4-week outpatient study in which patients were allowed to dose contingent upon approval from an Interactive Voice Response System (IVRS). We note that 7 subjects, 5 on zolpidem (3.3%), and 2 on placebo (1.4%), dosed after reporting that they had less than 4 hours of time in bed remaining. In addition, while the study was not designed to detect patients who spent less than 4 hours in bed after dosing, morning calls to the IVRS system suggested that at least 2% of patients in each week of the study were presumably out of bed less than 4 hours after dosing. These

[1] Leufkens TR, Lund JS, Vermeeren A. *Highway driving performance and cognitive functioning the morning after bedtime and middle-of-the-night use of gaboxadol, zopiclone and zolpidem.* J Sleep Res. 2009, Jun 22.

apparent dosing errors are of particular concern because if such errors occurred in the highly ordered setting of a controlled trial, it is reasonable to presume that in actual clinical use the risk of similar mis-dosing could be higher, potentially greatly so. We recognize that there was no correlation in Study ZI-12 between dosing with less than 4 hours remaining in bed and adverse events, but the power of the study to detect such correlation was extremely limited.

While we recognize that inadvertent re-dosing was not definitively identified in Study ZI-12, a high percentage of unaccounted-for doses of Intermezzo occurred, which we believe may be the result of re-dosing errors. Subjects were given a 2-week supply of study medication, and unused tablets were counted on return clinic visit. About 15% (22/150) of zolpidem patients had a deficit of ≥4 tablets from the expected number based on the IVRS record. This percentage would raise concern for re-dosing errors even if no different than the placebo arm, but in fact a lower percentage, 8% (12/145), in the placebo arm had such a deficit. Both zolpidem and sleep itself are known to interfere with memory, increasing concern for inadvertent re-dosing. In addition, it is not clear that normal human forgetfulness, unassociated with other factors, would not present a meaningful risk of inadvertent re-dosing, particularly for a drug like Intermezzo that is taken on an irregular schedule.

You submitted an amendment on May 29, 2009, containing arguments that MOTN dosing is no more likely to cause medication errors (i.e. double dosing or misjudging the available time remaining to sleep) than traditional HS dosing. Concerning the amnestic properties of zolpidem, you argue, based on a 1997 study by Mintzer et al. (Behavioural Pharmacology, 1997), that the low dose of zolpidem in Intermezzo would not cause memory impairment. However, you acknowledge that memory impairment from 3.5 mg zolpidem was measured in study ZI-05-009 in your development program. You appear to dismiss the relevance of this positive finding by stating that memory impairment was only statistically significant at 20 minutes after dosing, a time when sedation from Intermezzo would be near maximum, and presumably when most patients would be asleep. However, we do not believe that study ZI-05-009 was capable of excluding clinically meaningful memory impairment beyond 20 minutes. Critically, the data from Study ZI-12 documents that that Intermezzo does not prevent subsequent MOTN awakenings, such that opportunity for re-dosing error appears to occur at later times during the night when the patient is awake after the initial Intermezzo dose.

You further argue that patients with insomnia are hyper-aroused, and therefore less vulnerable to sleepiness-related impairments in memory. However, the extent to which hyper-arousal overcomes sleepiness-related and/or drug-induced memory impairments is not clear, and neither is any possible effect of hyper-arousal on 'ordinary' human forgetfulness about medication dosing.

Your amendment also addresses the fact that falling back to sleep itself is associated with amnesia; events occurring within 5 minutes of falling asleep are more difficult to remember than events occurring more remotely from falling asleep. You note that about 1% of doses of Intermezzo in your study were followed by sleep onset within 5 minutes, potentially increasing the risk that patients would not remember if a dose was taken. While we agree that not all patients that fall asleep within 5 minutes of dosing will take another dose on subsequent

awakenings, in the context of a drug that is taken nightly or near-nightly on a chronic or chronic intermittent basis, it is not clear that the risks are even smaller than 1% can be readily dismissed.

In addition, as discussed with you on several occasions, our concerns about re-dosing during the night are heightened because, with your current proposed packaging, patients will not be able to determine whether or not they have administered a dose should they wake up subsequent to a treated episode of awakening.

Finally, in your amendment you propose to mitigate any remaining concerns about dosing errors by the following actions:

1. Medication Guide
    - Revise the medication guide to include more prominent language concerning potential MOTN dosing concerns, (b) (4)
    - Affix the medication guide (b) (4)

2. REMS
    - Submit a REMS plan to track the effectiveness of the Medication Guide (on July 1, 2009, we acknowledge that you submitted an amendment containing the REMS, consisting of a Medication Guide and Knowledge, Attitude, and Behavior [KAB] Survey).

3. Pharmacovigilance measures
    - Routine pharmacovigilance will include enhanced reporting for spontaneous adverse events (AEs) attributed to medication errors.

4. Phase 4 study
    - You agree to develop, in collaboration with the Agency, a Phase 4, health system database study/survey to evaluate any potential AEs associated with middle-of-the-night use of zolpidem tartrate sublingual tablet.

We considered these mitigation proposals, but found them to be inadequate. We are not convinced that increasing the prominence of warning language in the Medication Guide is likely to reduce any cause of mis-dosing, and particularly to reduce *inadvertent* mis-dosing, which by nature occurs because patients have forgotten or misjudged the dosing situation. While the REMS, pharmacovigilance measures, and Phase 4 study may provide more information about safety risk, the information by definition would not be available until after approval, and thus these activities do not contribute to the necessary pre-approval safety evidence for Intermezzo.

The division communicated to you some of the above concerns about your May 29, 2009 amendment during a second teleconference July 24, 2009. In response to our continued concerns about the dosing compliance issues, you responded in an amendment dated July 30, 2009 with a proposal (b) (4)

(b) (4)

In terms of possible paths forward, the division believes that additional data on the effects of Intermezzo on driving could potentially clarify safety. First, it appears necessary for you to more clearly establish that Intermezzo, when taken as directed, does not unacceptably impair driving ability. Second, it appears necessary for you to demonstrate that dosing errors can be adequately minimized, or that the potential adverse effects of such dosing errors on driving safety are acceptable. We acknowledge that the published studies of zolpidem in driving are not definitive, but find that without additional data we can not conclude that Intermezzo can be reliably used safely.

In addition, alternative packaging that might markedly decrease the possibility of inadvertently taking a second dose (or perhaps even prevent dosing if the patient has less than 4 hours of sleep remaining) would be useful.

We would be happy to discuss possible study designs and/or alternative packaging that might address the above concerns.

**LABELING**

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If you have any questions, call Cathleen Michaloski, MPH, Sr. Regulatory Project Manager, at (301) 796-1123.

Sincerely,

*{See appended electronic signature page}*
Russell G. Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-22328 | ORIG-1 | TRANSCEPT PHARMACEUTICALS INC | ZOLPIDEM TARTRATE LOZENGE |

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

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/s/

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RUSSELL G KATZ
10/28/2009