

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21029

ADMINISTRATIVE DOCUMENTS

MINUTES OF MEETING

DATE: November 17, 1994

DAY: Thursday

TIME: 1:30-3:30pm.

PLACE: room 2064 Woodmont II

SUBJECT: Studies to support an NDA

DRUG: temozolomide

IND: / /

SPONSOR: Schering

PARTICIPANTS:

FDA: Dr. Temple, Dr. Justice, Dr. Krook (ODAC member by speaker phone if available) Dr. Schechter, Dr. Wilson, Dr. Koutsoukos, Dr. Mehta, Dr. Kaus, Dr. Ludden, Mr. Zimmerman, CSO,

SPONSOR: See package

The purpose of the meeting was to discuss the future development in terms of pivotal trials and the population pharmacokinetic study for temozolomide. The firm proposes to do a Phase 2 study in (Glioblastoma Multiforme (GBM) at first relapse after radiation and definitive surgery (\pm chemotherapy). It will be a US multicenter randomized trial with a "reference agent", procarbazine, with 100 patients/arm (200 total). The temozolomide schedule is daily x5d every 4 weeks. Procarbazine will be given daily x 28d every 56 days. The primary endpoint is rate of progression free survival (PFS) at 6 months. PFS is time from initial treatment with study drug until progressive disease or death. Overall survival will also be determined. QOL data would be collected using a neuro-oncology module which the sponsor states has been validated at _____ on approximately 100 patients.

The firm also proposes to conduct two separate uncontrolled studies (in AA and GBM) with 100 patients in each study. The

second GBM study will be conducted in Europe.

Dr. Levin presented background information about GBM including response to therapy at relapse, the difficulties of measuring brain tumors, and the problems with using neurological progression without radiological confirmation to define progressive disease.

A long discussion about the role of the reference agent (procarbazine) and the relation of a "reference study" to an equivalence study, etc. ensued. The firm suggested that the procarbazine arm would be a "prospective historical control" and would attempt to validate historical data and identify what procarbazine can do in this disease using 1994 methods and technology. Dr. Temple, Dr. Justice and Dr. Schechter expressed concern about this type of trial design. A randomized two arm comparative study was felt by the FDA to be a better design. The company stated that there are inadequate patient numbers for this type of design. The company was advised by Dr. Temple that problems would arise should procarbazine have a more favorable effect when the response to both agents was poor ($\leq 20\%$ PFS @ 6 months). The company indicated that they understood the problems with the proposed design.

A discussion about using time to neurologic symptoms as an endpoint ensued. Dr. Levin noted that he prefers to use an objective method such as tumor measurement because neurologic progression is not always due to tumor. The British CRC Study in brain tumors which demonstrated a 50% response rate did not use scans (tumor measurements) but only neurologic symptoms as an endpoint. Therefore, the true response rate to temozolomide cannot be determined.

The progression free survival (PFS) at 6 months for no treatment is near zero. Dr. Temple advised that it would be important to establish a complete database about progression free survival with/without treatment.

The firm proposed to use the UCSF historical database to establish a 6 month progression rate. The Agency noted that the firm has the burden of providing convincing data to FDA and to the Advisory Committee regarding the UCSF and other historical

databases in terms of an accurate estimation of progression and progression free survival at 6 months.

Regarding an excipient change in the drug product, the firm noted that the MTD will be established soon with this new formulation. the MTD appears to be about 1000 mg/mL. There has been no change in toxicity profile and blood levels are comparable between the old and new formulations.

Validation of the EORTC Quality of Life scale and the neuro module were presented and discussed. The EORTC QOL instrument has been used in Europe. The sponsor stated that the neuro module has been used and validated at

The firm presented their plan for a population pharmacokinetic study. Phase 1 data from 18 patients were used to generate times to obtain blood samples which will be between 1.5 and 4 hours post dose. Two groups will be used with different sampling times in this time frame. The firm noted that the assay is specific for temozolomide. The possibility of the active metabolite was discussed. The study will be controlled for food (fasting 2 hours before and 4 hours after dosing) to ensure accurate PK data. Ondansetron usage and the effect on PK was discussed. Regarding use of a standard antiemetic regimen, the firm noted that minimal antiemetics have been required. Dr. Ludden suggested using the 18 patient data to simulate 300 patients. In addition to the target sampling times, the actual sampling time should be recorded and, if possible, some late samples in the 6 to 8 hour range should be obtained. The firm should also consider some second cycle sampling. Enhancing compliance can be aided by visiting the sites. Dr. Mehta suggested that the sponsor should consider correlating temozolomide PK with its toxicity and/or efficacy. The sponsor said they were planning to do this.

After the meeting the firm was requested to provide copies of all overheads and information provided on slides.

cc:

Orig IND

Div File

HFD-150/RJustice

HFD-150/GSchechter

HFD-150/SWilson

HFD-150/TKoutsoukos

HFD-150/PZimmerman/11-18-94/12-14-94/6-19-95

HFD-426/MMehta

HFD-713/LKaus

R/D init. by TKoutsoukos/12-19-94

LKaus/11-21-94/12-19-94

MMehta/11-21-94

GSchechter/12-5-94

RJustice/6-17-95

General requirements for Biopharmaceutics submission :

1. A mass balance study to determine the disposition of the drug in humans.
2. Metabolic profile of the drug should be characterized. The enzymes involved in the biotransformation should be identified. The activity of the metabolites should be determined.
3. A general descriptive assessment of the pharmacokinetic parameters (C_{Max} , $t_{1/2}$, AUC, clearance, volume of distribution etc.) of the drug at the therapeutic dose, preferably in the target population.
4. Provide studies showing dose proportionality within the dose range recommended in the labeling.
5. In general the Division of Biopharmaceutics requires establishment of bioequivalence between the clinical and the production batches, if formulation and/or manufacturing techniques are different between the two batches.
6. Assay for the drug as well as its active metabolites should be validated in terms of its specificity, limit of quantitation, sensitivity, accuracy and precision including both intra-assay and inter-assay variability.
7. The batches used in bio studies and the proposed production batch should be properly identified in terms of, formulation, batch size, lot number, date of manufacture, expiration date etc.
8. Units of measurement to express various pharmacokinetic parameters in different studies should be consistent in the submission.
9. A detailed statistical report should be presented and two one-sided test procedure with 90% confidence interval should be used on log transformed data for any type of bioequivalence assessment.
10. Composition of the meal used in food effect study should be properly documented in terms of calories, fat, protein, carbohydrate contents, etc.
11. The sponsor is encouraged to characterize enzymatic pathways, specially the P-450 family involved in drug biotransformation and study various potential drug interactions derived from preclinical and in vitro studies.

12. Drug disposition in special populations where appropriate, like hepatic and renal impaired, geriatric, and pediatric populations should be studied, specially, if certain population is particularly likely to be exposed to the drug.

13. Plasma protein binding of the drug and its metabolites over the therapeutic range of concentrations should be determined.

14. Evaluation of a pharmacokinetic and pharmacodynamic relationship is strongly recommended.

15. The effect of gender and age on the pharmacokinetics of the drug should be analyzed.

**APPEARS THIS WAY
ON ORIGINAL**

MEETING MINUTES

MEETING DATE: June 18, 1998

TIME: 12:00 pm

LOCATION: Conf. Rm. E

IND

Meeting Request Submission Date: April 16, 1998
Briefing Document Submission Date: May 29, 1998

DRUG: Temodal (temozolomide) Capsules

SPONSOR/APPLICANT: Schering Corporation

TYPE of MEETING:

1. Pre-NDA and CANDA proposal
2. Proposed Indications:
(Glioblastoma multiforme), anaplastic astrocytoma (and metastatic malignant melanoma)

FDA PARTICIPANTS:

Dr. James Krook - ODAC Consultant
Dr. Robert Temple - Director, Office of Drug Evaluation I (Industry meeting only)
Dr. Robert Justice - Acting Director, Division of Oncology Drug Products
Dr. John Johnson - Medical Team Leader
Dr. Liang Zhou - Chemistry Team Leader
Dr. Xiao Hong Chen - Chemistry Reviewer (pre-meeting only)
Dr. Nallaperumal Chidambaram - Chemistry Reviewer (pre-meeting only)
Dr. Wendy Schmidt - Pharmacology Reviewer
Dr. Tony Koutsoukos - Biometrics Reviewer
Dr. Atik Rahman - Biopharmaceutics Team Leader (pre-meeting only)
Dr. Lydia Kieffer - Biopharmaceutics Reviewer
Mr. Gary Gensinger - Computer Specialist (pre-meeting only)
Mr. Patrick Guinn - Project Manager

INDUSTRY PARTICIPANTS:

Dr. Jonathan Spicehandler - President, SPRI
Dr. Cecil Pickett - Executive Vice President, SPRI
Dr. Robert Spiegel - Sr. Vice President, Medical Affairs
Dr. Marco Taglietti - Vice President, Clinical Oncology
Dr. Joseph Lamendola - Vice President, U.S. Regulatory Affairs
Dr. Sarah Zaknoen - Clinical Project Director
Dr. Uwe Fraas - Associate Director, Clinical Research
Dr. Harold Amkraut - Director, Biostatistics
Dr. Sudhakar Rao - Project Leader, Biostatistics
Dr. David Sugano - Director, Pharmacoeconomics

IND

Meeting Minutes

Page 2

Mr. Ross Lobell - Associate Director, U.S. Regulatory Affairs

Dr. Henry Friedman - Consultant, Duke University

Dr. Michael Atkins - Consultant, Beth Elizabeth Cancer Center, Boston, MA

MEETING OBJECTIVE:

To discuss the preclinical and clinical data which will form the basis of the planned August 1998 NDA submission for Temodal in the treatment of glioblastoma multiforme, anaplastic astrocytoma and metastatic malignant melanoma.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. Does the Agency agree that the data are sufficient to support an NDA for glioma?
 - The data may be sufficient to support an NDA for (GBM). The data is not sufficient to support an NDA for Anaplastic Astrocytoma. A randomized control trial is required for full approval for Anaplastic Astrocytoma.
 - Accelerated approval may be possible for recurrent anaplastic astrocytoma with no alternative therapy. You should provide a case that there are no alternative therapies and consider what would be the confirmatory study.
 - It is not clear how supportive (I94-122 will be for GBM) and how supportive C/I94-123 will be for Anaplastic Astrocytoma because they are uncontrolled.
2. Does the Agency agree the data are sufficient to support an NDA for (Metastatic Malignant melanoma)?
 - The data may be sufficient to support an NDA for (Metastatic Malignant Melanoma)
3. Are there any special concerns the Agency would like to have addressed in the NDA?
 - We would like a detailed explanation of how tumor volume and tumor area are calculated. We would like sufficient data in the MS Access DB so that the FDA can do its own calculations of tumor volume and tumor area for each patient at each tumor assessment.
 - In the GBM study, since the advantage of progression free survival is one month, it will be important for the Agency to determine when individual patients were followed for progression and to confirm the determination of progression. (How often were the patients

evaluated?)

- In the (melanoma) study, you will need to address the magnitude of effect of DTIC on progression free survival as well as overall survival (i.e., review and summarize the literature).
- Are you planning to do longitudinal analysis on QOL data?
 - ◊ Yes. There will be further discussion with the statistician.
- Clinical Pharmacology and Biopharmaceutic concerns based on the Clinical Pharmacology summary submitted:
 - a. More than one patient will be required to document the penetration of temozolomide into the CSF and to support any claims in the labeling.
 - ◊ Collection of data is on-going.
 - b. Has a link addressing the bioavailability between the CRC and the Schering formulation been established?
 - ◊ There are no direct studies comparing AUCs. The pre-clinical studies were done using the Schering formulation. Schering will provide additional clarification.
 - c. Urinary excretion is a significant pathway for temozolomide elimination and it appears that the final degradation product of temozolomide is uric acid which is renally eliminated as well, therefore, the data addressing renally impaired patients performed with temozolomide should be provided.
 - d. Has the sponsor addressed the penetration of temozolomide into the CSF of pediatric patients and compared the results to adult patients?
 - ◊ No.
 - e. We remind the sponsor that all dissolution information should be included in the submission as previously discussed with the Agency.
 - f. Electronic data transmission information format will be forwarded to the sponsor.

- g. Additional recommendations for NDA submission will also be forwarded to the sponsor.
- h. Does the sponsor intend to submit the PK results from studies I95-018, C/194-123, (194-122, and C94-09)?

No Yes

4. Does the Agency have any suggestions with regard to the proposed CANDAs database structure and reviewer aids?

- An Annotated CRF with all Access DB field names for each datapoint on the CRF should be included in the NDA.
- A Dictionary should be included in the NDA defining all field names and defining all codes in fields of the Access DB.
- All Access DB Tables should have a unique patient identifier in a single field.

◊ Schering will check on this.

- On pages 195 and 200 of the briefing Book, how are Qualitative and Quantative Tumor Measurement different?
- On page 200 what are axial area and slice measurement?

5. Additional FDA Request

- An all electronic NDA removes the requirement to submit an Archival Copy of the NDA in Hard copy. However, the Medical Officer will need the following reviewer materials in hard copy: All Protocols and all Study Reports (including Tables and individual patient Data Listings).
- The Biopharmaceutics Reviewer and Biostatistician would like the Protocol, Study Reports, Tables and Summaries in hard copy.
- All Disciplines would like the summary volume to be in hard copy.
- The Pharmacologist would like to have the non-clinical studies being submitted for the first time in hard copy.

- The Chemistry Reviewer would like to have the Chemistry Section in hard copy.

ACTION ITEMS:

1. There will be further communication between Schering and Dr. Koutsoukos regarding statistical issues.
2. Schering will provide further explanation regarding a link addressing the bioavailability between CRC and the Schering formulations.
3. Electronic data transmission information format regarding PK data will be forwarded to Schering.
4. Additional Biopharmaceutics recommendations for NDA submission will be forwarded to Schering.
5. Schering will comment on whether all Access DB Tables have a unique patient identifier in a single field.

The meeting was concluded at 1:30 pm. There were no unresolved issues or discussion points.

 / S /
Patrick Guinn, Project Manager
Minutes preparer

Concurrence Chair:

 / S /
John Johnson, M.D.
Medical Team Leader

6-20-98

IND
Meeting Minutes
Page 6

cc:
Original IND
HFD-150/Div File

Electronically only cc:

R Temple
R Justice
J Johnson
L Zhou
X Chen
N Chidambaram
W Schmidt
T Koutsoukos
A Rahman
L Kieffer
G Gensinger
P Guinn
L Vaccari
D Pease

MEETING MINUTES

Quinn

MINUTES OF TELECON

DATE: April 18, 1997 Time: 11:00a.m. - 12:00p.m. Location: Conf B

IND #: DRUG: Temodal (temozolomide) Capsules

Indication: Anaplastic Astrocytoma(Metastatic Colorectal Carcinoma/Glioblastoma Multiforme/Advanced Cancer)

SPONSOR: Schering-Plough Research Institute

PURPOSE: To discuss the QoL statistical analysis issues for the proposed initiation of Phase III clinical studies.

FDA PARTICIPANTS:	Clare Gnecco, Ph.D.	-- Biometrics Team Leader
	Tony Koutsoukos, Ph.D.	-- Biometrics Reviewer
	Masahiro Takeuci, Ph.D.	-- Biometrics Reviewer
	Patrick Guinn	-- Project Manager

Sponsor Participants:

- Dr. Nick Pellicione
- Dr. David Sugano
- Dr. Wayne Weng
- Dr. Sudhakar Rao

Meeting Objectives:

1. To address the questions about the QoL analysis plan for the (194-122 GBM) study.
2. To address the issues for the (C/I 94-091 (GBM)) study regarding the QoL comparisons between Temozolomide and Procarbazine.

DECISIONS (AGREEMENTS) REACHED:

A. (194-122 GBM) study.

1. Do the 6 month event-free survivors differ from the non-survivors at baseline?

→ Although these two groups have similar HRQL scores at baseline, 6-month event-free survival cannot be predicted. Therefore, HRQL cannot be used as a primary endpoint but can serve as a secondary endpoint.

- Schering-Plough needs to define "completers/dropouts". If the patterns over time of "completers/dropouts" are similar in both groups, then all the data can be used. If there is a difference in pattern between "completers/dropouts", then the data needs to be evaluated separately for the "dropouts" and "completers".
2. What does the 6-month event-free survival mean in terms of HRQL benefits ?
- This information could show positive changes from baseline and would be used for Descriptive Guidelines.
3. What are the key HRQL scales? What is meaningful change in HRQL scores for a patient?
- It was discussed that there would be 7 key HRQL scales that would be considered. The following key scales were selected: role functioning, social functioning, global HRQL, visual disorder, motor dysfunction, communication deficit, and drowsiness.
 - The Sponsor suggested that a 10 point shift would be considered as clinically significant.
4. What is the association between clinical and HRQL responses?
- The Sponsor understands that the numbers of responders are small but feel the trend is going in the right direction. Therefore, the Sponsor would like to use HRQL responses for descriptive purposes in regard to the percentage of patients achieving an HRQL response within Complete/Partial Response, Stable Disease, and Disease Progression groups.
5. Are HRQL improvements due to increase in steroid use?
- The study shows that there were some effects attributable to steroid use but manifested mainly as a size reduction of the tumors.

→ Schering-Plough also agreed that other factors (concomitant medications) could be potential confounders. These other factors such as mood altering drugs (antidepressants, tranquilizers) should be evaluated. The other factors were not evaluated previously because only the effects of steroids were being concentrated on at that time.

6. Can we describe the extent of HRQL improvement across the 7 key scales?

→ Schering-Plough has decided that all 7 key scales hold the same significance and therefore, the 7 net scales will be summarized as net overall global endpoint, not as separate endpoints.

B. For the (C/I 94-091 (GBM)) study, HRQL comparisons between Temozolomide and Procarbazine.

1. Baseline comparison between treatment groups.

→ Schering-Plough will compare all domains of the 7 key scales and sub-group's based on baseline comparability.

2. Comparison between 6-month event-free survivors from each treatment arm.

→ The Sponsor suggested that a 10 point shift would be considered as clinically significant. This information could show positive changes from baseline and would be used for Descriptive Guidelines.

3. Comparison of HRQL response in the 7 key scales between treatment groups:

a) % of responders between groups

→ It was agreed that this is only a secondary endpoint and would only provide a Descriptive Analysis.

b) duration of response between groups

- It was recommended by the FDA that a formal longitudinal model (i.e. GEE or Laird/Ware methods, etc.) should be employed to assess missing data patterns and time trends in the quality of life data.
- It was also agreed that Schering-Plough will define "completers/dropouts". If the patterns over time of "completers/dropouts" are the same within each treatment group then the data will be analyzed in aggregate by treatment group. However, if the patterns over time of "completers/dropouts" are different for each group, then the "dropouts" will be compared between the two treatment groups and the "completers" will be compared between the two treatment groups separately.
- It was also agreed that Schering-Plough will provide censoring patterns for each group in the NDA submission to identify information on patterns of missing data.

4. For each patient, his/her median and best scores of change from baseline during treatment will be determined. We will compare the median score and best score between treatment groups. This comparison can also be performed within each clinical response subgroup (CR/PR, SD, DP).

- The Agency recommends avoiding this approach because it doesn't take into consideration the amount and type of missing data.
- The Agency also recommends a formal longitudinal analysis as in 3.b.

5. Q-TWiST analysis: Quality-adjusted survival analysis using the Q-TWiST methodology will attempt to integrate the information on toxicity, response and progression in terms of quality-adjusted time in each of these defined health states. An overall comparison of the two treatment arms using the Q-TWiST method will be attempted.

IND
page 6

cc: Original IND
Div. File
HFD-150/GSchechter
HFD-150/JJohnson
HFD-710/MTakeuchi
HFD-710/TKoutsoukos
HFD-710/CGnecco
HFD-150/PGuinn/drafted 5-14-97

R/D init. TKoutsoukos/5-19-97
CGnecco/5-16-97

F/T by PGuinn/5-19-97

MINUTES OF TELECON - Statistical ISSUES

MEETING MINUTES

DATE: October 8, 1996

DRUG: Temodal (temozolomide) capsules

IND #:

SPONSOR: Schering-Plough Research Institute

PARTICIPANTS:

- | | | |
|--------------------------------|----|-------------------------------|
| FDA: Robert DeLap, M.D., Ph.D. | -- | Division Director |
| James Krook, M.D. | -- | ODAC |
| John Johnson, M.D. | -- | Medical Team Leader |
| Genevieve Schechter | -- | Medical Reviewer |
| Atiqur Rahman, Ph.D. | -- | Biopharmaceutical Team Leader |
| Wendy Schmidt, Ph.D. | -- | Pharmacology Reviewer |
| Tony Koutsoukos, Ph.D. | -- | Biostatistician |
| Gary Gensinger | -- | Operations Research Analyst |
| Paul Zimmerman | -- | Project Manager |
| Patrick Guinn | -- | Project Manager |
| Schering: Dr. Dugan | -- | Clinical Research, SPRI |
| Dr. Resnick | -- | Clinical Research, SPRI |
| Dr. Pickett | -- | Discovery Research, SPRI |
| Dr. Osoba | -- | Prof. Med., CAN |
| Dr. Prados | -- | Prof. Med., UCSF |
| Dr. Pai | -- | Biostatistics/Pop. PK, SPRI |
| Dr. Amkraut | -- | Biostatistics, SPRI |
| Dr. Rao | -- | Biostatistics, SPRI |
| Dr. Sugano | -- | Pharmacoeconomics, SPRI |
| Dr. Pellicione | -- | Regulatory Affairs, SPRI |
| Mr. Lobell | -- | Regulatory Affairs, SPRI |

ISI
11/7/97

SUBJECT: Pre-NDA Meeting requested by the Sponsor

PURPOSE: To discuss the data available for a New Drug Application for Temodal.

BACKGROUND INFORMATION:

11-17-94

A meeting was held to discuss the future development in terms of pivotal trials and the population pharmacokinetics study for temozolomide.

The sponsor also proposed to conduct two separate uncontrolled studies (in AA and (GBM)) with 100 patients in each study.

The FDA recommended a randomized two arm comparator study and advised the Sponsor that problems would arise should the procarbazine have a more favorable response when the response to both agents was poor ($\leq 20\%$). The Sponsor indicated that they understood the problems with the proposed design.

Using time to neurologic symptoms as an endpoint was discussed and it was decided that the true response rate to temozolomide cannot be determined in this manner.

The FDA advised the Sponsor that it would be important to establish a complete database about disease free survival with/without treatment. The sponsor proposed to use the UCSF database to establish 6 month progression rate.

The EROTC Quality of Life scale and neuro model was presented and appear validated.

The Sponsor presented their plan for a population pharmacokinetics study. The FDA advised the Sponsor to use the 18 patient data to simulate 300 patients; in addition to the target sampling times, the sponsor should consider correlating temozolomide PK with its toxicity and/or efficacy.

08-12-96

Additional data for Pre-NDA meeting submitted (serial # 101) regarding:

1. Drug substance stability summary for two batches of drug substance with 18 months of data.
2. Drug product release testing summary.
3. Drug product stability summary.

IND

page 3

4. -Dissolution stability summary.

08-14-96

CMC pre-NDA meeting held to discuss elements of the CMC content of the NDA which may be submitted in December 1996.

Recorded in the Meeting Minutes were specific items for discussion and listed the Agency's requirements.

09-17-96

Summary data to support the Sponsor's proposed dissolution methodology was submitted (serial #111) regarding:

1. Ph solubility profile of drug substance.
2. Capsule dissolution profiles in different media.
3. Data generated using different agitation rates.
4. Dissolution profiles of clinical and to be marketed capsule batches.

10-03-96

A facsimile was sent to the Sponsor with concerns to be addressed at the pre-NDA meeting on October 8, 1996.

MEETING DISCUSSION:

The attendees introduced themselves around the room and Dr. Krook joined in via telephone.

The introduction of the meeting agenda was done by Dr. Pellicione of Schering-Plough Research Institute.

Dr. Dugan of Schering-Plough Research Institute presented the clinical data using the overheads (pages 7-20) provided a day in advance, which addressed the questions that were sent from us by facsimile transmission on October 3, 1996.

Dr. Sugano presented the Quality of Life section (overhead pages 21-24) which addressed Question #5 sent in the above mentioned facsimile transmission sent on October 3, 1996.

There were no follow up questions from the FDA regarding the presentations.

Two questions from the Sponsor were addressed.

1. Does the FDA agree that the data from the interim analyses of these clinical trials in these patient populations is sufficient to support an NDA submission?

The Agency feels that it would be premature to file for an NDA because only 25% of the randomized patients have been analyzed. There is already therapy approved for this indication. The information provided by the first interim analysis is not enough to support safety nor efficacy.

2. Does the FDA agree that the randomization to procarbazine should be stopped?

The Agency does not recommend closing this arm. Only 25% of the patients have been evaluated, no objective response has been observed in either arm of the study, and the time to event information may change with subsequent analyses.

The following questions/concerns were brought up by the FDA.

- > The overall survival is better for procarbazine than for Temodal.
- > The power of the trial is very low.
- > No CR/PR responses are observed on either arm.
- > Time to event endpoints are not evaluable without RCT. The patient cannot serve as his/her own control for time to event endpoints.
- > If the studies are not blinded, investigator bias may occur. Conclusions from trials which are not blinded/randomized are difficult to make with regard to time to event endpoints other than survival.

The Sponsor responded with the following comments.

- > The study was never designed to compare Temodal with procarbazine. Procarbazine was to be used as a concurrent "historical" control. The trial sample size is not large enough to demonstrate superiority with adequate statistical power.

- > The primary endpoint was to demonstrate 20% improvement in progression free survival at six months for temozolomide as compared to the historical reference agent procarbazine. Six month progression free survival is 7% for the procarbazine arm and 15% for the Temodal arm.
- > The confidence intervals around the 15% PFS will not narrow appreciably even with an increase in the patient number to 120/arm.

SUMMARY/ACTION ITEMS:

- > The FDA is supportive of continuation of the current studies to accrue more efficacy and safety data and quality of life information.
- > The Sponsor should communicate to the Agency the results of the next interim analysis to see if the data is adequate for NDA filing.
- > The Sponsor should discuss evaluation of Quality of Life information with Dr. Koutsoukos of the FDA.
- > The Sponsor is encouraged to characterize any palliative benefits to individual patients.
- > The Sponsor will prepare a CANDAs proposal and submit to Dr. Schechter for review.
- > Dr. Rahman will provide specific Biopharmacokinetic issues to be addressed by the Sponsor.
- > Dr. Schmidt will have follow up Discussions with the Sponsor on intrathecal indications.

IND
page 6

cc:ORIG. IND

Div. File

HFD-150/RDeLap

/JJohnson

/GSchechter

/JDeGeorge

/WSchmidt

/ETolgyesi

/PDietze

/ARahman

/LKieffer

/CGnecco

/TKoutsoukos

/GGensinger

/PZimmerman

/PGuinn/drafted 10-17-96

/DPease

R/D init by:

GSchechter/10-18-96

ARahman/11-19-96

WSchmidt/11-20-96

Tkoutsoukos/11-20-96

JJohnson/11-23-96

RDeLap/12-8-96

MEETING MINUTES

NDA 21-029 CMC 45 Day Meeting

Reviewer: Chengyi Liang

Date: 9/22/1998

NAME AND ADDRESS OF APPLICANT:

Schering Corporation
2000 Galloping Hill Rd.
Kenilworth, NJ 07033

DRUG PRODUCT NAMES:

Proprietary:

Temodal

Nonproprietary/USAN:

Temozolomide

Code Name/#:

CAS 85622-93-1

Chem. Type/Ther. Class

1-P

DOSAGE FORM/STRENGTHS:

250 mg; 100 mg; 20mg; 5mg/capsule.

ROUTE OF ADMINISTRATION:

Oral

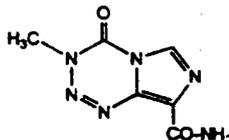
MANUFACTURER:

B. Drug Product
Schering Corp.
2000 Galloping Hill Rd.
Kenilworth, NJ 07033

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR WEIGHT:

3,4-Dihydro-3-methyl-4-oxoimidazo[5,1-d]tetrazine-8-carboxamide

$C_6H_6N_6O_2$, MW = 194.15



1. Drug Substance:

From 1992 to 1998, 29 lots of DS have been synthesized

2. Drug Product:

28 Batches of DP were manufactured as 4 strengths of capsules (5, 20, 100 and 250mg). The specifications of DP for each strength is provided including Assay (90-110%), Dissolution (Q = μ min), Total impurities (<1.2%), Uniformity of Dosage and Microbial Limits (total aerobic <1000 cfu/g; total yeast/mold <500 cfu/g). The stability studies were performed for each strength of DP capsule (4 batches for 5 mg; 4 batches for 20 mg; 5 batches for 100 mg and 4 batches for 250 mg). The data provided in NDA show that the DP is stable at 25°C/60%RH for 24 months.

CONSULTS:

Consult
EER
Trademark
Statistics
Biopharmaceuticals
Microbiology
Environmental Assessment.

Status	Comments
Pending	Submitted on 8/20/98
Pending	Submitted on 11/13/96
Pending	Submitted on 9/21/98
Pending	Submitted on 9/21/98
Pending	Submitted on 9/21/98
Categorical	Acceptable
Exclusion	

CONCLUSIONS AND RECOMMENDATIONS:

The NDA is fileable based on CMC standing points.

1 /SI/ 11
9/21/98

Chengyi Liang, Ph.D., Review Chemist

1 /SI/ 9/21/98

Liang Zhou, Ph.D.
Chemistry Team Leader

CC:
Orig. NDA 21029
HFD-150 Division File
HFD-150/CLiang
HFD-150/LZhou
HFD-150/PGuinn

OCT 29 1998

**45-DAY FILING REVIEW
CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS****NDA 21029****Submission Date: August 12, 1998**

Drug Name: Temozolomide (Temodal®)

Formulation: Capsule 5, 20, 100, and 250 mg

Sponsor: Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Reviewer: Lydia V. Kieffer, Pharm.D.

Type of Submission: New Drug Application

Temozolomide is an oral, alkylating, imidazotetrazine agent. Temozolomide is a prodrug and a 3-methyl analog of mitozolomide that undergoes non-enzymatic hydroxylation at physiologic pH and temperature to its active metabolite: 3-methyl-(triazene-1-yl) imidazole-4-carboxamide (MTIC). MTIC then spontaneously converts to the reactive methyl-diazonium ion and 5-aminoimidazole-4-carboxamide (AIC). MTIC is also believed to be the active metabolite of dacarbazine. The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA at the O⁶ and N⁷ positions of guanine. The sponsor's proposed indication is for the treatment of patients with malignant glioma (glioblastoma multiforme and anaplastic astrocytoma) at first relapse and metastatic malignant melanoma with recurrent small cell lung cancer.

According to tables A and B of volume 1.72 (Biopharmaceutics study summary), submitted studies include: One food effect study, 1 mass balance study, 1 drug interaction study, 1 study with plasma to CSF pharmacokinetic data, 4 Phase I studies, 7 Phase II studies, and 2 population pharmacokinetics analysis which included the Phase I and II studies mentioned. The 4 Phase I studies included 2 single dose/multiple dose studies, 1 multiple dose study, and 1 study with urinary excretion data. Further details on the Phase II studies is not evident thorough tables or an index in the hard copy.

Verification of the contents of summary tables E and F (dissolution testing/dissolution profile results, and proposed product dissolution method specification, respectively) is not possible due to lack of referencing.

Comments to the Sponsor:

The hard copy of the Biopharmaceutics section of the NDA is not indexed, paginated, and organized in a manner that will facilitate review of the material; however the electronic version does have an index. A hard copy of the index should be submitted to the Agency to facilitate review. The following deficiencies were noted:

1. Dissolution studies for the proposed specifications can not be found in the submission. The sponsor is required to submit the dissolution data as soon as possible for review.
2. Where would protein binding data be located in section 6 of the NDA?

Recommendations:

1. Please forward the above comments to the Sponsor.

**APPEARS THIS WAY
ON ORIGINAL**

N */S/*
Lydia V. Kieffer, Pharm.D.
Reviewer
Division of Pharmaceutical Evaluation I

/S/ *10/29/98*
Atiqur Rahman, Ph.D.
Team Leader
Division of Pharmaceutical Evaluation I

cc: Orig 21029
HFD-150/ Division File
HFD-150/ DCatterson, JJohnson, MCohen, PAndrews, WSchmidt, LZhou
HFD-850/ LLesko
HFD-860/ MMehta, ARahman, LKieffer
HFD-340/Vishwanathan
CDR BMurphy

Day 35 NDA Filing Review
NDA 21029
TEMODAL (Temozolamide)
Schering-Plough Research Institute

Submission Date: August 12, 1998

Reviewer: Martin H. Cohen, M.D.

Type of Submission: New Drug Application

Proposed indications for Temodal include:

1. Treatment of patients with metastatic malignant melanoma.
2. Treatment of patients with glioblastoma multiforme at first relapse.
3. Treatment of patients with anaplastic astrocytoma at first relapse. — *Designate as "P"*

To support the above indications 2 pivotal randomized trials (for patients with metastatic malignant melanoma and for patients with relapsed (glioblastoma multiforme) were submitted. In addition two supportive open label trials, for patients with relapsed glioblastoma multiforme and for patients with relapsed anaplastic astrocytoma were submitted. All of these studies are summarized below.

1. Pivotal Melanoma Trial (C94-091)

A multicenter international randomized trial in which 305 patients with metastatic malignant melanoma were randomized to receive oral Temodal daily times 5 every 4 weeks or intravenous dacarbazine daily times 5 every 3 weeks. Patient eligibility included histologic confirmation of diagnosis, performance status 0-2, measurable disease, no prior chemotherapy except for local limb perfusion without dacarbazine, no brain metastases and adequate laboratory studies. Tumor evaluations, by physical exam were done at each cycle of chemotherapy and tumor evaluation, by imaging studies, were performed every other treatment cycle.

The primary study objective was to compare overall survival of patients receiving the study drugs. Secondary objectives were progression free survival, objective response rates, health-related quality of life, pharmacokinetics of parent drugs and major metabolites, and population pharmacokinetics (for temazolamide only) at selected centers. Safety was assessed and hematologic and non-hematologic toxicity were graded using Common Toxicity Criteria.

Study Results were as follows:

1. Median overall survival (ITT analysis) was 7.7 months and 6.4 months for the temozolamide and dacarbazine treatment groups, respectively, $p = 0.20$. The hazard ratio was 1.18 (95% CI of 0.922 to 1.52).
2. Median progression free survival (ITT analysis) was 1.9 months and 1.5 months for the temozolamide and dacarbazine treatment groups, respectively, $p = 0.012$. The hazard ratio was 1.37 (95% CI of 1.07 to 1.75).
3. Response rates (CR + PR) were 13.5% and 12.1% for temozolamide and dacarbazine treated patients, respectively.
4. Temozolamide had an acceptable safety profile. The most commonly reported adverse effects (mostly mild to moderate in severity) included nausea, vomiting, pain, constipation, fatigue and headache. Grade 3 or 4 thrombocytopenia was reported in 20% of patients and grade 3 to 4 neutropenia in 22% of patients.

Pivotal Glioblastoma Multiforme Trial (C/194-091)

A randomized, multicenter, open-label phase II study of Temozolamide and reference agent (Procarbazine) in the treatment of patients with glioblastoma multiforme at first relapse.

Two hundred twenty five patients were randomized to receive temozolamide, daily times 5 orally, every 4 weeks or procarbazine daily times 28 orally, followed by a 28 day rest period. Pathology and radiology were centrally reviewed. Inclusion criteria included histologic confirmation of diagnosis, PS ≥ 70 , unequivocal evidence of tumor recurrence or progression after radiation therapy, and no more than one regimen of chemotherapy (including a nitrosourea), an MRI within 72 hours of a repeated resection and acceptable laboratory values.

The primary objective was to compare progression free survival at 6 months and safety for temozolamide and procarbazine. Secondary objectives were overall survival, health related quality of life, and population pharmacokinetics (Temozolamide patients only).

Study results were as follows:

1. The 6 month PFS was 21% (95% CI 13% to 29%) for Temozolamide and 9% (95% CI 4% to 15%) for Procarbazine $p=0.016$
2. Median PFS was 2.99 months and 1.97 months for Temozolamide and Procarbazine, respectively $p=0.0065$.
3. Median overall survival was 7.34 months versus 5.82 months favoring Temozolamide $p=0.337$.
4. The Q-TWiST analysis favored Temozolamide.

Supportive, open label glioblastoma trial. (C/194-122)

138 patients. PFS at 6 months was 19%. Thus supports pivotal study.

Supportive anaplastic astrocytoma trial (C/194-123),

162 patients. PFS at 6 months was 46%. Response rate included 13 CR's and 42 PR's.

Comments to sponsor.

1. In C94091 (Glioma pivotal trial) there is determination of tumor axial area and perpendicular volume at baseline by central reviewer (146 patients), tumor volume at baseline by central reviewer and determination of tumor area at baseline by site reviewer (207 patients). In evaluating progression free survival whose measurements did you use, which measurements did you use (volume or area) and in what priority order?

The same problem exists in the Anaplastic Astrocytoma trial C94123. There are 162 patients in the demographics table and 114 and 115 baseline patients in the Tumor volume by central reviewer and the Quantitative tumor measurements tables, respectively. There are 133 patients in the Baseline tumor measurement by site reviewer table. What algorithm did you use to determine tumor measurements for all study patients

2. In C94091 and C94123 tumor volumes are not the same in two tables recording central reviewer measurements (Quantitative tumor measurement from central reviewer [Perpendicular volume] and Tumor volume from central reviewer). Which should be used?

Recommendations

With data provided addressing the above comments a clinical review of the NDA can be accomplished.

Martin H. Cohen, M.D.
September 16, 1998

cc. NDA21029
Division File
Guinn

In the glioblastoma studies and in the anaplastic astrocytoma studies there are large numbers of patients without any scan assessments of their tumors in some of the Tables. For example in the anaplastic astrocytoma study the following Tables have different numbers of patients.

Demographics 164

Quantative Tumor Measurement from Central Reviewer 118

Tumor Area from Central Reviewer 152

Tumor Measurement from Site Reviewer 162

Which of these Tables did Schering use for determination of tumor progression and tumor response and if more than one Table was used, what was the priority?

If for example, the Quantative Tumor Measurement from Central Reviewer Table was used, were other Tables used for patients with missing data in this Table?

Also in the Table Concomitant Steroid Medications many dates are missing, so it is sometimes not possible to determine the start or end date for steroids. Please supply the missing dates if possible. If not, how did you deal with this in your analysis?

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: September 17, 1998

FROM: Patrick Guinn, Project Manager

SUBJECT: Schering Plough Research NDA 21-029 for Temodal (temozolomide) Capsules

TO: Central Document Room

NDA 21-029 Temodal (temozolomide) Capsules for the treatment of adult patients with malignant glioma (glioblastoma multiforme and anaplastic astrocytoma) at first relapse and as first line therapy for patients with advanced metastatic malignant melanoma, submitted August 12, 1998 and received August 13, 1998 will need to be split into three separate NDAs for administrative purposes. We are splitting this NDA according to its three indications because the review priority designations are different.

The original designation NDA 21-029 should be associated with the indication for the treatment of adult patients with anaplastic astrocytoma at first relapse.

Please assign two new NDA numbers for the other indications as indicated below. I have identified the indication on each 1.1 volume that is provided, by writing and highlighting it on the cover letter and 356H.

- For the treatment of adult patients with glioblastoma multiforme at first relapse.
- First line therapy for patients with advanced metastatic malignant melanoma.

Please return the 1.1 volumes to Patrick Guinn, Project Manager Division of Oncology Drug Products, HFD-150 when completed.

Although the NDA will be split into three separate applications, the archival copies of the NDA already submitted will not be separated out by indication, however, subsequent clinical submissions will be placed into the appropriate NDA. Subsequent chemistry, pharmacology and biopharmaceutics submissions should be placed in the original NDA 21-029 and cross referenced to the other NDAs. We will also inform the User Fee Division of the steps that we have taken.

Trade Name TEMODAL Capsules Generic Name temozolomide

Applicant Name Schering Corporation HFD - 150

Approval Date If Known: Pending Accelerated Approval for Anaplastic astrocytoma

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?
YES / X / NO / ___ /

b) Is it an effectiveness supplement?
YES / ___ / NO / X /

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / X / NO / ___ /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety? NO

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____
_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____
_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____
_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # ____ YES /___/ NO /___/ Explain: _____

Investigation #2

IND # ____ YES /___/ ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/

NO /___/

If yes, explain: _____

- /S/

2/4/99

Patrick Guinn
Project Manager

/Date

/S/

2/12/99

Robert L. Justice, M.D.
Acting Division Director

/Date

cc: Original NDA 21-029
HFD-150/Division File
HFD-150/PGuinn
HFD-93/Mary Ann Holovac

Patent Information Pursuant to 21 CFR § 314.53

RE: Temodal (temozolomide) oral capsules to treat patients with glioma (glioblastoma multiforme and anaplastic astrocytoma) at first relapse and patients with metastatic malignant melanoma

Tradename	Temodal®
Active Ingredient:	temozolomide
Strength:	150 and 200 mg per capsule
Dosage Form	Oral Capsules

Pursuant to the provisions of 21 C.F.R. §314.53, we are submitting the patent information for the captioned Schering Corporation ("Schering") NDA to include the following patent:

U.S. Patent No.:	5,260,291
Expiration Date:	November 9, 2010
Type of Patent:	A drug and drug product patent covering temozolomide as the compound per se (the active ingredient in TEMODAL), formulations containing temozolomide, and methods of using temozolomide for treating patients afflicted with glioma and metastatic neoplasm, including melanoma.
Patent Owner:	Cancer Research Campaign Technology Limited

The undersigned declares: (1) that U.S. Patent No. 5,260,291 covers (a) the compound temozolomide (the active ingredient in TEMODAL™), (b) the TEMODAL™ formulation, and (c) the method of using TEMODAL™ (temozolomide) to treat glioma and metastatic neoplasm, including melanoma; and (2) that the TEMODAL™ (temozolomide) product is the subject of this application for which approval is being sought under Section 505 of the Federal Food, Drug and Cosmetic Act.

The undersigned further declares that a claim of patent infringement could reasonably be asserted against a person not-licensed under U.S. Patent No. 5,260,291 who engages in the manufacture, use, sale, offer to sell or importation of the TEMODAL™ product.

The undersigned declares that this patent information, submitted in duplicate, is in full compliance with 21 USC §355(b)(1) and 21 C.F.R. §314.53.



SCHERING CORPORATION

2000 GALLOPING HILL ROAD



KENILWORTH, N.J. 07033

TELEPHONE: (808) 298-4000

August 10, 1999

Robert Justice, M.D.
Food and Drug Administration
CDER/Oncology Group (HFD-150)
Woodmont II Building (Room 2055)
1451 Rockville Pike
Rockville, MD 20852

NDA 21-029
SCH 52365
Temozolomide Capsules

SUBJECT: DEBARMENT CERTIFICATION STATEMENT

Dear Dr. Justice:

Enclosed please find the revised debarment certification statement for this application.

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j) as well as the FDA regulations.

Sincerely,

Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs

JA/bs

Debarment Certification:

In accordance with section 306(k) of the Food, Drug and Cosmetic Act, Schering Corporation certifies that, with respect to this application, it did not and will not use in any capacity the services of any persons that have been debarred under the provisions of Section 306(a) or (b) of the Act.

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	<u>21029</u>	Trade Name:	<u>TEMODAL (TEMOZOLOMIDE)</u>
Supplement Number:		Generic Name:	<u>TEMOZOLOMIDE</u>
Supplement Type:		Dosage Form:	<u>Capsule; Oral</u>
Regulatory Action:	<u>AE</u>	Proposed Indication:	<u>TEMODAL Capsules are indicated for the treatment of adult patients with anaplastic astrocytoma at first relapse.</u>

IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION? YES

What are the INTENDED Pediatric Age Groups for this submission?

 NeoNates (0-30 Days) Children (25 Months-12 years)
 Infants (1-24 Months) Adolescents (13-16 Years)

Label Status	<u>INADEQUATE Labeling for ALL PEDIATRIC ages</u>
Formulation Status	<u>NO NEW FORMULATION is needed</u>
Studies Needed	<u>STUDIES needed. Applicant has COMMITTED to doing them</u>
Study Status	<u>Required studies are ongoing</u>

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:
02-08-99 This has been approved under accelerated approval.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, PATRICK GUINN

Signature / S / _____ Date 2/8/99

MINUTES OF TELECON

MEETING DATE: July 8, 1999

TIME: 1:15 pm

LOCATION: Conf. Rm. B

NDA 21-029

DRUG: TEMODAR (temozolomide) Capsules

SPONSOR/APPLICANT: Schering Corporation

TYPE of MEETING:

1. Special – Guidance for Phase 4 study proposal to satisfy accelerated approval conditions
2. Proposed Indication: For the treatment of adult patients with refractory anaplastic astrocytoma, i.e., patients at first relapse with disease progression on a nitrosourea and procarbazine containing drug regimen.

FDA PARTICIPANTS:

Dr. Temple – Office Director
Dr. Justice – Acting Division Director
Dr. Beitz – Acting Deputy Director
Dr. Johnson – Medical Team Leader
Dr. Cohen – Medical Officer
Mr. Guinn – Project Manager

INDUSTRY PARTICIPANTS:

Dr Lamendola – Vice President, Regulatory Affairs
Ms. Aoyagi – Regulatory Affairs
Dr. Zaknoen – Clinical Research
Dr. Encraut - Biostatistician

BACKGROUND:

The proposed Phase 4 commitment to satisfy accelerated approval conditions was submitted June 24, 1999 and received by us on June 25, 1999.

MEETING OBJECTIVES:

1. To discuss the proposed Phase 4 study protocol submitted on June 24, 1999.
2. To discuss any outstanding NDA issues (labeling and Tradename).

DISCUSSION and DECISIONS REACHED:

1. Difference in schedule and dosing in the monotherapy arm versus the combination arm.
 - As currently proposed, the Agency does not think the combination arm of your protocol would provide useful information in addressing your Phase 4 commitments to satisfy the conditions of accelerated approval. However, if you were to revise your protocol to incorporate the same dosing schedule for the monotherapy arm and the combination therapy arm, you have the opportunity of showing additive effect.
 - The proposed dosing schedule is based upon Cooperative Group work outside of Schering. Schering will discuss the possibility of making the dosing schedule consistent between the monotherapy and combination arms.
2. Primary analysis plan.
 - As proposed, it appears that you are only considering beating an active drug, temozolomide versus BCNU, and not proposing to show additive effect, BCNU versus BCNU + temozolomide.
 - Currently, Schering intends to compare temozolomide versus BCNU as single agent therapies. If there is a significant difference, then Schering will compare the monotherapy versus the combination arm. Schering will provide a statistical plan proposal detailing the primary analysis plan clarifying the final analysis.
3. Safety data available to start the proposed combination therapy arm.
 - Prior to initiating the combination arm of the proposed study, Schering should provide any available data to support the safety of the proposed dosing schedule.
 - Schering will provide the Phase 1 data that is available to support the dosing schedule proposed for the combination arm.
4. Use of the proposed Tradename, TEMODAR.
 - The use of the Tradename TEMODAR for temozolomide capsules is acceptable.

ACTION ITEMS:

1. Schering will provide the Division with a summary of the Phase 1 data that supports the proposed dosing schedule in the combination arm.



DEPARTMENT OF HEALTH & HUMAN SERVICES

P. GUINN

Food and Drug Administration
Rockville MD 20857

NDA 21-029

Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

JUN 29 1999

Attention: Joseph Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs

Dear Dr. Lamendola:

We acknowledge receipt on June 25, 1999 of your June 24, 1999 resubmission to your new drug application (NDA) for Temodar (temozolomide) capsules.

This resubmission contains additional information regarding your proposed phase 4 study submitted in response to our February 12, 1999 action letter. We also refer to your amendments of February 11 and 22, April 23, and May 19 and 24, 1999 which were partial responses to our action letter.

We consider this a complete class 1 response to our action letter. Therefore, the primary user fee goal date is August 25, 1999 and the secondary user fee goal date is October 25, 1999.

If you have any questions, contact Patrick Guinn, Project Manager, at (301) 827-1537.

Sincerely,

/s/

6-29-99

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:

Archival NDA 21-029
HFD-150/Div. Files
HFD-150/P.Guinn
DISTRICT OFFICE

f/t by: dwp/June 29, 1999

CLASS 1 RESUBMISSION ACKNOWLEDGEMENT (AC)
(DDR: Update the user fee goal date based on the class of resubmission.)

Guina

OCT 13 1998

Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Attention: Joseph F. Lamendola, Ph.D.
VP Regulatory Affairs

Dear Dr. Lamendola:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Temodal Capsules (temozolomide) 5, 20, 100, 250 mg, Oral
for the treatment of adult patients with anaplastic astrocytoma

Therapeutic Classification: Priority (P)

Date of Application: August 12, 1998

Date of Receipt: August 13, 1998

Our Reference Number: 21-029

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 12, 1998 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be February 13, 1999.

We have determined that this application will be reviewed under 21 CFR 314 Subpart H (accelerated approval). We remind you that as required under 21 CFR 314.550, unless otherwise informed by the Agency, you must submit for Agency review before approval of this application copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days after marketing approval.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.