Health Canada / Santé Canada

Contact: Policy_Bureau_Enquiries
Telephone: 613-948-4623
Fax: 613-941-1812

EXPERT ADVISORY COMMITTEE ON BIOAVAILABILITY AND BIOEQUIVALENCE

RECORD of PROCEEDINGS

Therapeutic Products Directorate Note: Until such time as final recommendations are made and policy is developed and published, current bioequivalence requirements remain unchanged.

Teleconference April 16, 2003

Committee Members Present: Dr. J. Thiessen (Chair), Dr. J.G. Besner, Dr. R. Herman, Dr. F. Jamali, Dr. R. Nair, Dr. E. Palylyk-Colwell, Dr. W. Racz, Dr. K. Renton, Dr. W. Riggs, Dr. D. Sitar, Dr. F. Varin, Mr. S. Walker

Regrets: Dr. A. Donner, Dr. M. Kara, Dr. J.N. McMullen,

Health Canada (HC) Participants: M.M. Bernard (BMORS*), L. Cockell (DBE*), G. Condran(BPS*), L.N. Cui (DBE), M. Davis (EAC Secretariat Officer, PB*), C. Ficker (DBE), J. Gordon (DBE), A. Makinde (DBE), C. Pereira (EAC-BB Coordinator, PB), C. Simon (DBE), S. Stojdl (DBE), A. Tam (DBE), P. Wielowieyski (DBE)

*Abbreviations for Health Canada (HC) Bureaux/Divisions and other terms used in this record:

BMORS	=	Bureau of Metabolism, Oncology and Reproductive Sciences
BPS	=	Bureau of Pharmaceutical Sciences
DBE	=	Division of Biopharmaceutics Evaluation (BPS)
PB	=	Policy Bureau
BA	=	Bioavailability
BB	=	Bioavailability & Bioequivalence
BE	=	Bioequivalence
EAC - BB	=	Expert Advisory Committee on Bioavailability & Bioequivalence

➤ **ITEM 1 - Roll Call, Conflict of Interest (COI), & Agenda Review** (J. Thiessen)

The Chair welcomed the members and briefly outlined the format for this teleconference. He reminded the members that since this was in essence a continuation of the March meeting, their conflict of interest declarations were still valid. The only item to be discussed will be Levothyroxine from the March agenda.

➤ **ITEM 2 - HC Presentation on Levothyroxine**
*Is Levothyroxine Sodium a Critical Dose Drug?***** (P. Wielowieyski)
(**Powerpoint presentation available upon request)

A short presentation was made giving some background information and posing three main questions to the EAC. The questions will be quoted below with the EAC's final recommendations for each one.

➤ **ITEM 3 - Deliberation of Questions** (Members)

The discussion covered a variety of issues, such as:

- effect of small changes in T4 on T3
- variability of TSH, particularly within an individual
- sensitivity of TSH when suppressed
- variability in assay methods such as radioimmunoassay
- endogenous hormone levels
- sensitivity of T4 to detect differences between formulations
- need for titration in levothyroxine dosing
- harmonization with US and EU requirements for levothyroxine
- diurnal variation in endogenous levels
- methods of baseline correction
- number of strengths to be studied given that eleven strengths are currently marketed (25, 50, 75, 88, 100, 112, 125, 150, 175, 200 and 300 µg)

This list is by no means exhaustive and is intended only to give a sense of the type of issues discussed.

➤ **ITEM 4 - EAC's Final Recommendations** (Dr. J. Thiessen)

Question 1

Is levothyroxine sodium a critical dose drug?

"those drugs where comparatively small differences in dose or concentration lead to dose- and concentration-dependent, serious therapeutic failures and/or adverse drug reactions which may be persistent, irreversible, slowly reversible, or life threatening events."

Yes, levothyroxine is a critical dose drug. Concern was expressed with respect to adverse effects, for example, potentially life-threatening cardiac effects as a result of aggressive treatment of elderly patients who are hypothyroid. The US FDA's (Food & Drug Administration) classification of this drug as a narrow therapeutic range drug was also taken into consideration.

Question 2

Is levothyroxine sodium a drug with a narrow therapeutic range (NTR)?

Report C

"A drug with a narrow therapeutic range is one which commonly exhibits adverse effects which limit the therapeutic use in doses close to those required for the therapeutic effect. When there is a known relationship of plasma concentrations to therapeutic and toxic effects, the ratio of the lowest concentration at which clinical toxicity commonly occurs to the median concentration providing a therapeutic effect would not be greater than 2."

The EAC did not consider levothyroxine to be a NTR drug because the ratio of the lowest concentration at which clinical toxicity commonly occurs to the median concentration providing a therapeutic effect would be greater than 2 and therefore it would not fit the NTR definition in Report C. However, levothyroxine should be classified as a critical dose drug and until such time as bioequivalence criteria for critical dose drugs are defined, current bioequivalence standards for NTR drugs should be applied to levothyroxine.

Question 3

In light of the recent FDA deliberations, is baseline-corrected total T4 an appropriate and sensitive measure?

T4 is the preferred measure, T3 is an active metabolite, and TSH is a 'downstream' biomarker that is considerably more variable

Doses of 600 µg or greater should be utilized in healthy volunteers, as concentrations are significantly higher than the individual subject's baseline T4 values.

Healthy volunteers (allows for the use of a single dose study, more sensitive evaluation of true formulation differences)

Total T4, without a baseline correction, is insensitive for bioequivalence analysis.

The committee came to consensus on the following statements:

- ***T4 is an acceptable marker for rate and extent of absorption.***
- ***T4 alone should be used as a measure of comparative bioavailability.***
- ***A baseline correction is recommended.***
- ***Three appropriately spaced pre-dose samples are recommended, for baseline correction for endogenous T4. The FDA guidance with respect to sampling times is acceptable.***
- ***A 600 µg dose should be used. Greater than 600 µg may increase risk of cardiac complications. Testing of more than one strength is recommended. Strengths should be chosen so as to adequately bracket the proposed range of strengths***
- ***Healthy volunteers should be used in testing.***
- ***Current TPD requirements call for sampling to 72 hours for long half-life drugs. For levothyroxine, the FDA recommends sampling for 48 hours. The committee considered sampling over a 48 hour period to be adequate, in part because of the reduced suppression of endogenous levels after that time and the reduced reliability of the recommended baseline correction method over a longer sampling period.***

➤ **ITEM 5 - HC Announcements concerning next meeting (June 2003)** (C. Pereira)

HC is planning on having a stakeholder workshop and EAC meeting in June. Work is currently underway towards completion of discussion papers, which will be posted to the HC website before the meeting. The topics for the June meeting are:

- Highly variable drugs
- Fed BE studies

An invitation to participate has been posted on the web site and will also be sent to stakeholder organizations. Stakeholders are invited to attend the meeting as observers or to make short presentations on either/both of the two issues. More details can be found on the HC website at

http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/bb_jun03_web_announce_e.html

➤ **ITEM 6 - Meeting Adjourned** (J. Thiessen)

Next Meeting: Workshop June 26, EAC deliberations June 27, 2003
Prepared by: M. Davis and C.Pereira
2003-07-07