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MINUTES

Team Meeting „NCE Incontinence"

August 10,1998

Participants:	Hilmar Boekens	Claus Meese
	Peter Ney	Dietrich Schacht
	Bengt Sparf	Christoph Arth (part time, TOP 5)

Distribution: Participants, Lars Ekman, Ulrike Kluge

Agenda:

1) Chemistry	- upscale - status of synthetic routes - isomer synthesis - enantiomers separation	(C. Meese)
2) Biological	- bioavailability dog	(H. Boekens)
3) Milestone decision	- Selection of lead compound family	(team)
4) Pharmacology	- definition of Panlabs screen	(P. Ney)
5) Miscellaneous	- patch development	(C. Arth)

Ad 1) For details see handout of C.O. Meese „Chemical Development Plan - Update 7" (attachment 1). It is obvious that the availability of pure enantiomers of the prodrugs is still critical. Issues are addressed and first positive results have been reported by the external experts.

Ad 2) H. Boekens explained the results of the bioavailability study (attachments 2). As expected, the oral bioavailaility of SPM 8163 (metabolite) dropped further after lowering the dose 1µmol/kg. The experimental part of the study was finalized at LPT on July 20, 1998. (Post Meeting note: Draft report from LPT arrived August 13, 1998).

Ad 3) After intense discussions it was decided to move forward the OH-/-OCOR compounds. Main reasons are:

- easy and quick metabolization in vitro by S9 mix and/or microsomes
- relatively good chemical stability
- reasonable bioavailability in dogs

It is expected that further modifications of the ester moiety may lead to a relative bioavailability of about 50%.

Ad 4) A reasonable outline of selected tests as well as budget outline will be prepared on availability of the enantiomers. The decision, which substances have to be included will be taken at this time (next meeting).

Ad 5) C. Arth presented the first data on in vitro penetration through hairless mouse skin as well as human skin. This first shot with not yet optimized formulations revealed very good and promising results (attachment 3). PRIVILEGED

PRIVILEGED

Actions until next meeting

- Enantiomer synthesis and/or racemate separation	(C. Meese)
- Optimization of bioanalytical method	(H. Boekens)
- Follow up preclinical program e.g. receptor screen	(P. Ney)
- Follow up patch development	(C. Arth, C. Meese)
PRIVILEGED	(CA, COM, PN, DS)

Next meeting: September 30 - October.2, 1998; the exact date will be communicated by P. Ney asap.

Peter Ney
Monheim, August 21,1998

attachment 1

SCHWARZ PHARMA

Chemical Development Plan

Incontinence Project

Aim: Synthesis of prodrugs

Update (7) June 26 - August 10, 1998

Highlights

Scale-up (P&U route)	SA's are available with all custom manufactures: SELOC France (former SICOR), step 6 being completed on a lab scale, evaluation of hole synthesis is ongoing, step 6 is offered for ca. 650 TDM/6 months as of October. SIFA (ca. 400 TDM/18 months) and Dynamit Nobel (ca. 400 TDM/6 months as of October) assessments are also made for step 6. AlliedSignal: documentation not yet transferred.
Syntheses (P&U route)	re-synthesis of step 3 (100g, Fa. Thalmann) for resolution (see below), compound expected CW 34.
Synthetic alternatives:	Heck-Cuprate route (cooperation with MPI Mülheim): step 3/5 being completed. Reformatski (ongoing, inhouse).
Enantiomers	chiral HPLC separations were successful on almost all steps, step 6 is going to be separated on a 20g scale (CW 33, Chiral Technologies/France). chiral separation of hydroxy metabolite: enantiomers successfully separated by capillary electrophoresis (coop. with Prof. Blaschke/Münster). Chemical resolution is possible on the acid of step 3 by the combinatorial approach of Prof. Wijnberg/Univ. Groningen/NL (planned for CW 34 on a 100g scale).
Dog Studies	to be reported by H. Bökens.
Patch development	to be reported by C. Arth.

Lowlights

Enantiomer resolution according to the P&U patent is still irreproducible (step 6).

Intrinsic instability of a phenolic monoester has been detected after four months at room temperature (interconversion to di-ester and hydroxy metabolite).

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