Minutes SDZ ENA 713 TDS LTS-SANDOZ Working Group Meeting
November 28, 1995, Basel

FK Hr. Dr. Asmussen
Dr. Herstmann
Dr. Schnabel
Dr. Hoffmann
Dr. v. Kleinsorgen
Dr. Meyer
Dr. Schwarz
17.02.96
ort ma.

date minutes: 22.1.1996

Participants LTS:
Mr. B. Asmussen, PhD (R&D)
Mr. K. Köpke, PhD (R&D)

Participants Sandoz:
Ms. K. Bergmann, PharmD* (DDS-CH)
Ms. I. Fortis (Quality Assurance and Documentation-CH)
Mr. O. Garinot, PhD (Analytical R&D-F)
Mr. F. Richter, PhD (Head Drug Delivery Systems-CH), part-time,
Mr. J. Ogorka, PhD (Technical Research and Development, representative of International Project Team)
Mr. H. Tiemessen, PhD* (Drug Delivery Systems-CH)
* minutes

SUMMARY

The formulation program which was carried out by LTS has led to the conclusion that α-tocopherol (in concentrations even below 0.15%) is an appropriate antioxidant/stabilizer for the SDZ ENA 713 TDS. The amounts of degradation products were shown to be reduced by a factor of five to ten in stress stability tests (TDS at 60°C in primary packaging).

Levels of the two main residual monomers, ethylhexylacrylate (EHA) and acrylic acid (AA) were measured by Sandoz France. Preliminary results: EHA levels: 0.3% (0.17 mg /10 cm^2 TDS) in the active TDS and about 0.9% in the placebo. These levels are comparable to the values measured by LTS.

Measurement of residual monomers in commercial nicotine TDS (Nicopatch®, Pierre Fabre, FR; Nicotinell®, Zyma-Ciba, DL; Nikofrenon®, Hefa Pharma, DL) led to values of EHA which were slightly higher (0.17-0.28 mg /10 cm^2 TDS) than those in active SDZ ENA 713 TDS.

Preliminary results of acrylic acid measurements by Sandoz were not in accordance with the LTS results. Sandoz: 0.10% (active) and 0.13% (placebo); LTS: 0.01% (active) and 0.04% (placebo). The values, as obtained by the Sandoz method, of the Nicotine TDS were more than three times higher.

These results confirm the statement of LTS that 0.5% levels of residual monomers are in the usual range of marketed TDS products. However, the Working Group proposes to develop a back-up variant with lower levels of residual monomers in order to reduce the loss of time in case clinical studies would reveal local intolerance due to the adhesives present in the current TDS formulation (see below).

Furthermore, **the adhesive properties of the present formulation** have not yet been tested in man. LTS representatives expressed their concerns that the adhesive properties of the present formulation might be insufficient, particularly after an application period of 24 hours which is associated with a 30-40 % reduction in the drug content of the TDS. In the event of a reformulation, this aspect should be taken into account.

Therefore it is proposed to amend the technical development plan as follows:
1) Manufacture and release of active and placebo TDS with the current formulation modified

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

by addition of α-tocopherol (0.15%) and having equal levels of residual monomers (both active and placebo around 0.3% EHA). These TDS will be shipped under quarantine to Sandoz France (Orléans) on 5.2.1996. These TDS will be available (including packaging and shipment to the clinical center) for use in clinical studies W151 (cumulative irritation) and W152 (sensitization / irritation) on March 5, 1996.
The level of 0.15% α-tocopherol may be higher than in the final formulation but was selected to be on the safe side. The minimal required level of α-tocopherol will be determined by stress tests carried out in parallel.
Additional cost: 125'000 DM

2) Development of a back-up variant having i) a lower level of residual monomers and ii) better adhesive properties. The first TDS of this variant can be available at LTS by end of April, 1996. Additional cost: 90'000 DM.
Post minute Note: upon request of Sandoz, LTS agreed to prepare a preformulation plan for this activity.

3) The validation activities for the present formulation will be postponed until the results of the cumulative irritation study (W151) are known. The manufacture of the pilot batch (for registration stability) could be postponed to mid June 1996 (after the skin sensitization study is completed) without delaying the manufacture of the clinical supplies of the pivotal trials.

Further it is recommended to carry out a skin adhesion study in volunteers as early as possible, since this is not presently part of the clinical program (in all initial studies the TDS is secured by an adhesive tape) and insufficient adhesion properties are a no-go criterium for any TDS formulation.

The date of the next WG meeting has still to be fixed.

APPROVED:
LTS
name , date 22.2.96

Sandoz
name , date Dr. F. Richter
Pharmaceutical Development
Bau 340 / 705 ✆ 324 3421
F. Richter, 22.1.96

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

0. PERSONNEL

Ms K. Bergmann has changed her position within Sandoz Pharma she will no longer be directly involved in the SDZ ENA 713 TDS project. The working group thanks her cordially for her enthusiastic support of the WG and all her contributions.
The position of Sandoz project representative in the WG will be taken over by Mr Jörg Ogorka. We wish him success in this position and look forward to a good cooperation.

I. STRESS STABILITY TESTING OF STABILIZED VARIANTS

Because of the occurrence of unacceptable levels of degradation products in the TDS after storage, a formulation program has been carried out to investigate the factors which may have an influence on the degradation process and stabilizers which may slow down or stop the degradation. TDS samples were stressed at 60°C in primary packaging.
Since the stress stability data obtained from solutions were not considered to be indicative (in both directions) of the stability of ENA in a TTS formulation, it had been decided to conduct the stability studies with TDS.

Compared to the ambient atmosphere, oxygen increased the degradation process (about 1.5-2 times in 4 weeks) whereas a nitrogen atmosphere reduces the degradation rate clearly (2.5-5 times). These results confirm that the degradation process is of oxidative nature (Annex 1).

The comparison of different antioxidants regarding their stabilizing properties revealed that ascorbyl palmitate and combinations of α-tocopherol and ascorbyl palmitate were less effective than α-tocopherol alone. EDTA (acid) alone had only a minor effect and combinations of EDTA and α-tocopherol were not more effective than α-tocopherol alone (Annex 2).
From the stabilizers tested α-tocopherol appeared to be the best antioxidant/stabilizer for the SDZ ENA 713 TDS. The results have shown that α-tocopherol levels of 0.1% and 0.13% gave the same results and that higher concentrations do not lead to better stabilization effects (Annex 3).

In an other set of formulation tests is was shown that the degradation rate is independent of the level of residual monomers present.(Annex 3: "1753 redissolv.)" has a strongly reduced level of residual monomer because of extensive drying.
An alternative acrylate polymer (Durotak 901-1051) and polyisobutylene showed degradation patterns which are comparable to the present formulation. However, a silicone type of TDS formulation showed accelerated degradation of the active ingredient (Annex 4).

It can be concluded that α-tocopherol is the appropriate antioxidant/stabilizer for SDZ ENA 713 TDS in concentrations below 0.15%. However, the question if a lower level of α-tocopherol would suffice remains to be solved in a new stability program.

For the forthcoming clinical batches which have to be manufactured on short notice, a 0.15 % level of α-tocopherol will be used to be on the safe side. It is felt that no local tolerability studies need to be repeated if the content of antioxidant is reduced in a later development phase. Therefore it will be possible to reduce later this 0.15% level if future stability data support this.

For the validation of the optimal amount of α-tocopherol, LTS will prepare samples which will be stressed and analyzed by Mr Garinot. The results will be available by mid of May.

Since it cannot be excluded that the levels of individual degradation products exceed the value of 0.1% upon storage, it has to be considered to qualify the degradation products (toxicological test) 213-95 and 802-95. J. Ogorka will discuss this issue at the forthcoming Sandoz internal

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

project team meeting.

II. RESIDUAL MONOMERS

Mr Garinot had received the GC method from LTS to determine the levels of the two residual monomers ethylhexylacrylate (EHA) and acrylic acid (AA) in TDS. It was not possible to quantify the methylacrylate (MA: too broad peak) and the glycidylmethylacrylate.
The GC method needs to be modified and validated.
SDZ France has determined the contents of the residual acrylic monomers in the SDZ ENA 713 TDS and in commercially available nicotine patches.

The results obtained (Annex 5) are very similar to those from LTS for EHA. For the SDZ ENA 713 TDS batch used in the 4-week Tox. study, the EHA levels amount to 0.30% (active) and to 1.0% (placebo).
Preliminary results of AA measurements are not in accordance with the LTS results: 0.10% (active) and to 0.13% (placebo), LTS values: 0.01% (active) and to 0.04% (placebo). This discrepancy needs to be explained.
Mr. Garinot follows this issue up and report on his findings by 4/96.

Compared to the competitors nicotine TDS, the results of the active ENA TDS are in the same range for EHA (≈ 0.2 mg/TDS). However the placebo TDS contain significantly more EHA (0.6 mg/TDS) than the competitors (≈ 0.3 mg/TDS).
This result is a reason to take care that for future placebo batches the drying process is modified in such a way that the residual monomer levels will be in the same range (0.3-0.4%) as the active TDS in order to prevent false positive results in the local tolerability tests.

The results confirm the statement of LTS that 0.5% levels of residual monomers are in the usual range.

"Low residual monomer back-up"
However, because of the tox results in mini pigs, Sandoz still has concerns about the tolerability of the current formulation. Therefore, the start of the development of a back-up variant with less residual monomers is proposed in order to reduce the loss of time in case clinical studies would reveal skin tolerability problems with respect to the adhesives used in the current TDS. (see below)
LTS recommends not to try other polymer types because of reportedly worse skin tolerability properties or bad loading capacity (silicones). The back-up variant will contain (cross linked) polyacrylates, but will have lower levels of residual monomers. Sandoz considered it to be appropriate to restrict the individual levels of residual monomers to < 0.1 %. In the back-up formulation program several levels of α-tocopherol will be tested.

III. ADHESION PROPERTIES

The adhesive properties of the present formulation have not been tested in man. It is therefore possible that the adhesive properties of the present formulation are insufficient, particularly after an application period of 24 hours which is associated with a 30-40 % reduction in the drug content of the TDS. Further, a skin adhesion study in volunteers, which is presently not part of the clinical program (in all initial studies the TDS is secured with adhesive tape), is recommended to be carried out as early as possible.

When a low residual monomer back-up ENA 713 TDS variant is developed, as proposed by the

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

WG, at the same time the improvement of the adhesive properties will be a major aspect of this development. The fact that the drug content reduces significantly during the wearing period has to be taken into account.

The determination of the adhesive force (in-vitro test) as part of the stability program (batches 8/21093/055 and 8/21094/055) indicates that the alteration of this quality characteristic with time is acceptable if the TDS is stored at 4 °C (Annex 6).

IV. ANALYTICS

IV.1 Results of FTIR-study

The results of the ATR-FTIR-spectroscopy experiments with the aim to identify each individual component of the SDZ ENA 713 TDS were reported by Mr Schnabel (15.11.95).

- The ATR (attenuated total reflection) technique is a very economic method because no sample preparation is necessary: after being placed on the ZnSe-crystal the spectrum can be recorded immediately.
- FTIR spectra from the matrix dominated by the Durotak 1753.
- The active TDS shows some additional bands which are characteristic for the drug substance.
- Plastoid B could not be detected by FTIR although the active TDS is containing 20% of Plastoid B.
- The protective foil (release liner) and the backing foil can be easily identified. The obtained spectra can be compared with previously recorded and archived spectra of the corresponding foils.

IV.2 Stability data of TDS generated by Sandoz

The 6-month stability data on the first two active batches confirmed the degradation observed after 3 months: the main degradation product (213-95) amounts to approx. 0.3% at 25°C and to approx. 0.7% at 40°C; the sum of unknown degradation products amounts to approx. 0.4% at 25°C and to approx. 1.1% at 40°C (802-95 is taken as unknown degradation product as long as its accurate UV response factor is not determined).

Annex 7 shows the content of residual ENA 713 base in the pouches upon storage. There is a small but significant, temperature dependent leakage ("cold flow") of active ingredient from the matrix.

IV.3 Requirements for *in vitro* drug release

In order to take into account each individual value from each vessel for the drug release as requested by USP, SDZ proposes new release and control limits (see Annex 8).
Post meeting note: As discussed with Mr Garinot, LTS will maintain the established limits for drug release for the testing of the next batches (QI/96). The proposal of Sandoz will be discussed at the next meeting.

The 6-month stability data from SDZ ENA 713 TDS show a slight decrease of the release rate of the active ingredient after storage at 40°C/75% r.h. (approx. 5% less than the initial value after 23 hours).

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.