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Memorandum

DATE: 4.29.02

FROM: Douglas C. Throckmorton, M.D., Division Director
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SUBJECT: Approvability of Nitroglycerin ointment (Cellegesic) for anal fissures
NAME OF DRUG: Nitroglycerin Ointment
TRADE NAME: Cellegesic
IND/NDA: 21-359
FORMULATION: Ointment for topical administration

RELATED APPLICATIONS: Multiple oral and topical preparations of nitrates.
APPROVED INDICATIONS: None
SPONSOR: Cellegy Pharmaceuticals, Inc.

DOCUMENTS USED FOR REVIEW:

1. Division of Scientific Investigations Review by Antoine El-Hage, Ph.D., dated 3.15.02.
2. Medical and Statistical Review by Stephan Fredd, M.D., and James Hung, Ph.D., dated 2.27.02.
3. Clinical Pharmacology and Biopharmaceutics Review by B. Nhi Nguyen, Pharm.D., dated 3.12.02.
4. Pharmacology Review by Anthony G. Proakis, Ph.D., dated 4.10.02.
5. Chemistry Review by William C. Timmer, Ph.D., dated 4.19.02.
6. NDA 21-359 volumes 4.011 and 4.012.

CONCLUSIONS

This memorandum represents the Secondary Medical Review and the Divisional Memorandum regarding the approvability of Cellegesic for the treatment of anal fissures. At this time this memorandum is submitted, the product has been withdrawn, and no action is necessary; the intent of this memorandum instead is to summarize the thinking of the Division at the time of the withdrawal. As discussed below, this application was considered not approvable. The deficiencies are discussed by discipline in the following paragraphs.

PHARMCOLOGY TOXICOLOGY

It is clear that nitroglycerin (NTG) is effective at relaxing the anorectal smooth muscle in animals, providing the basis for a possible effect in patients with anal fissures, where chronic spasm of the anal sphincter is posited to lead to tissue hypoxia, pain and poor wound healing. There is also an effect of NTG to cause vasodilation, although the relative contribution of this mechanism to possible healing is unknown. In rats, administration of nitroglycerin produced a dose-dependent reduction in anal pressures, with no evidence of the development of tolerance. Regarding the pharmacology, toxicology, carcinogenicity of nitroglycerin, the sponsor submitted the NDA under the provisions of section 505 (b)(2), and referenced the Agency's previous findings related to nitroglycerin. Here, while the literature suggests some animal toxicological findings (*e.g.*, mutagenesis in one bacterial strain, testicular tumors in rats) there is evidence that the systemic exposure following topical anal administration is substantially lower than that seen using currently approved topical nitrate creams for angina. No deficiencies related to the pre-clinical Pharmacology or Toxicology were identified.

MEDICAL/STATISTICAL

On the basis of extensive published literature suggesting a robust, albeit variable, effect of topical nitrates in promoting both healing and reduction in pain associated with anal fissures, the sponsor conducted two clinical trials in sequence.

The first trial, NTG 98-02-01, evaluated 360 patients with anal fissures, who were administered one of six doses of nitroglycerin (NTG) ointment or placebo. The primary endpoint of the study was anal fissure healing, and the sponsor failed to demonstrate a signficant effect of Cellegesic compared with placebo. There was a nominally significant effect of Cellegesic to reduce the pain associated with the anal fissure when analyzed using a post-hoc statistical method.

On the basis of the secondary analysis, the sponsor conducted a second pivotal trial of NTG ointment, NTG 00-02-01, that randomized 229 patients to receive either placebo or NTG ointment (0.75 mg or 1.5 mg total dose per day). The primary endpoint of the trial was pain relief, assessed using a visual analogue scale (VAS) ranging from zero (no pain) to 100 (most severe imaginable). The protocol pre-specified a mixed regression model as the statistical analysis to be conducted on the ITT population for the primary endpoint. When this model was used, incorporating the parameters used in the first trial (98-02-01), no significant effect of Cellegesic on pain was demonstrated. While the incorporation of additional factors, including a quadratic effect of time and the effect of center, results in a nominally significant effect on pain, this analysis suggests an effect of Cellegesic on pain that is significant, at most for 1-2 weeks.

Unfortunately, there are no additional clinical benefits of the use of Cellegesic that were demonstrated (or strongly suggested) by the studies (see the Medical/Statistical review for details). For instance, no effect on anal fissure healing was demonstrated in either trial. There are also no available data on the possible effects of Cellegesic on the need for surgery for anal fissure (which is apparently the final procedure when necessary) or on any Quality of Life indices. The latter measure would be useful in defining the overall changes in functional status that are associated with the use of Cellegesic, and help to understand the balance between the proposed effects on the pain associated with anal fissures and the headache pain associated with the pharmacologic effect of nitroglycrin use.

The safety review raised no new issues of clinical safety relative to the extensive safety database available for topical nitrates. The major 'safety' issue that impacts the approvability decision is the need to understand the clinical consequences of the headaches caused by nitrates, as discussed above.

Based on the reviewed data, then, two Clinical/Statistical deficiencies were identified: insufficient evidence of effectivness in the treatment of patients with anal fissures, and insufficient data on the relative balance between the potential therapeutic effect of Cellegesic on anal fissure pain and the documented headache pain resulting from systemic absorption of NTG.

CHEMISTRY AND MICROBIOLOGY

The drug substance is commercially available, as SDM-27, and consists of 10% nitroglycerin (glyceryl trinitrate, NTG) in propylene glycol. This mixture complies with the current USP monograph. The drug product is described in the Chemistry review (page 12 of 36) and consists of SDM-27 combined with white petrolatum, lanolin, propylene glycol, paraffin and sorbitan sequioleate. Per the review Chemist, the acceptance criteria are appropriate to ensure the identity, strength, quality, potency and purity of the drug product as formulated. The drug product is to be packaged with two unique container-closure systems: one a collapsable aluminum tube, the second a metered-dose pump. No issues related to this packaging were identified in the Chemistry review (see section II.6). Two microbiology-related tests of the drug product were conducted: anti-microbial effectiveness test and total aerobic microbial count. As the product is petrolatum-based it dose not support microbial growth due to inadequate water content.

On the basis of the submitted stability data, the approved shelf life for Cellegesic ointment is 24 months for the NTG ointment in the aluminum tubes and is 12 months for the NTG ointment packaged in the metered-dose pump.

The following deficiencies were noted in the Chemistry review of the NDA submission:

1. The retest date for the drug substance needs to be specified.

2. Regarding test KABS-0038-LC, the impurities in the quantitative analysis of the nitroglycerin ointment are reported with no acceptance criteria. One set of all-encompassing physico-chemical tests should be developed for the finished dosage form to function as regulatory specifications as well as stability specifications. The tests should include an assay that reports the percentage of drug substance as well as impurities/degradation products. A limit needs to be developed for each impurity, as well as for the total impurity limit. These limits apply to impurity testing of the drug substance, release testing after manufacture of the ointment, and stability of the drug product.

3. As a part of the stability program (In-Process Controls and Tests), a numerical acceptance criterion needs to be developed for the viscosity test.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

The sponsor referenced the Agency's previous findings related to nitroglycerin under the provisions of section 505 (b)(2) for the clinical pharmacology of NTG. The clinical pharmacology of nitroglycerin has been described in other products using various dosage forms. These literatures adequately support an effect of NTG to dilate both arterial and venous systems and to relax smooth musle. In the present submission a single study (98-02-02) of the absorption of nitroglycerin following intra-anal administration. Study 98-02-02 was conducted in 6 healthy subjects (4 men, 2 women) and measured concentrations of glyceryl trinitrate (NTG) and two active metabolites. As the full details validating the measurement of NTG concentrations was not submitted in the NDA, the Biopharm reviewer was unable to draw final conclusions about the pharmacokinetics of NTG in the 6 patients, but there was clear evidence of systemic absorption of NTG. The bioavilability of NTG was approximately 50% following single and multiple dosing (page 25 of 28). The lack of analytic validation was identified as a deficiency.

COMPLIANCE

At the time of this letter the inspections by the Office of Compliance have not yet been completed. Given the length of time anticipated until the sponsor can obtain and submit a complete response to the deficiencies noted above, the request for inspections has been withdrawn.

SUMMARY

The overall weight of the evidence suggests, but does not demonstrate, that Cellegesic has some effect to ameliorate the pain of anal fissures. This impression is based on a series of post-hoc analyses of the data from the two pivotal trials conducted by the sponsor; analyses that require clinical confirmation through the conduct of additional clinical trialing using pre-specified endpoints and methods of analysis. No data on more durable clinical endpoints (*e.g.*, anal fissure healing, need for surgical intervention) are available to buttress the case for approval, although such data would be supportive and should be collected in any future trials. The case for approval of Cellegesic is made more difficult by the presence of a prominent side-effect of systemic nitrates: headache. Without direct data (*e.g.*, Quality of Life scales), the sponsor has asserted that relief of anal fissure pain more than offsets the >50% observed rate of headaches in the patients taking Cellegesic. Such data would add materially to the case for approval. Finally, a number of issues have been raised by the Chemistry, Biopharmaceutics reviewers that must be addressed by the sponsor. Given the uncertainty of the clinical effects, and these deficiencies, this NDA submission cannot be approved without additional clinical data.

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/s/

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MEDICAL OFFICER