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APPLICATION NUMBER: NDA 20582/S001

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

NOV 17 1998

Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation II

NDA: 20582/S-001

Drug: Follistim™ (follitropin beta for injection)

Sponsor: Organon

Date of Submission: 11/04/98

Type of Submission: BA/BE waiver request supporting change in diluent

Reviewer: Venkateswar R. Jarugula, Ph.D.

SYNOPSIS

Reference is made to the approved NDA 20-582, for Follistim™, which is indicated for the development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology (ART) program. Sponsor submitted a supplement (S001) on 5/18/98 to support a change in diluent from 0.45% NaCl to Sterile Water for injection, USP (WFI). Sponsor claims that this change is intended to improve the patient comfort during drug administration via subcutaneous or intramuscular injection. In a letter dated 09/10/98, FDA asked the sponsor to either conduct a bioavailability/bioequivalence study or request a biowaiver by providing scientific rationale for not conducting such a study.

In the current submission, the sponsor provided the biowaiver request along with the rationale for waiver (see Attachment I). According to the information included in the submission, dissolving 75 IU follistim in 1 ml of 0.45% NaCl results in isotonic solution (approximately 300 mOsm/kg) while the same in water for injection would result in a tonicity of 152 mOsm/kg. The sponsor claims that except for this difference in osmolality, the two parenteral solutions are identical.

The sponsor submitted results of a multiple dose, dose proportionality pharmacokinetic study, which was submitted to the original NDA, to show that the bioavailability of FSH is not affected following administration of 1, 2 or 3 cakes of 75 IU dissolved in 1 ml of 0.45% NaCl (resulting in osmolality ranging from 293 to 577 mOsm/kg). The results of this study indicate that a difference in tonicity by a factor of 2 has no influence on the bioavailability of FSH (see Attachment for PK results). A comparison of the tonicity values for 1, 2 or 3 cakes of 75 IU dissolved 0.45% and water for injection (WFI) is given in the table below:

Dose dissolved in 1ml	Osmolality	
	0.45% NaCl	WFI
1x75 IU	293	152
2x75 IU	435	295
3x75 IU	577	432

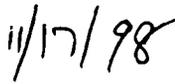
As shown in the table, except for the 75 IU, the range of tonicity values after dissolving 2 or 3 cakes in WFI fall within the range for 0.45% NaCl. Thus sponsor concluded that changing the solvent from 0.45% NaCl to WFI would have no effect on bioavailability of follitropin beta.

Reviewer Comment

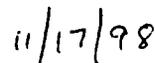
- The results of the multiple dose study referenced in the current submission prove that the bioavailability of follitropin is not influenced by the changes in tonicity by two fold and changes in concentration of active ingredient by three fold.
- Although the tonicity of the 75 IU follistim dissolved in WFI (152) falls out of range (293 to 577) of that observed for 0.45% NaCl and tested in multiple dose study, it is unlikely that a tonicity of 152 mOsm/kg (in WFI) will affect the bioavailability when 435 and 577 mOsm/kg of tonicity (in NaCl) did not affect the bioavailability.
- The pharmacokinetic parameters of Follistim dissolved in 0.45% NaCl are similar to those observed for Gonal-F (another approved product for follitropin) in water for injection (see Labeling for Gonal-F). Therefore, it is reasonable from pharmacokinetic perspective to conclude that the proposed change in diluent will not significantly affect the bioavailability of follistim.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II has reviewed the NDA 20-582/s-001 dated 11/04/98 and recommends that biowaiver can be granted based on the information provided in the submission.



 Venkateswar R. Jarugula, Ph.D.

RD initialed by Ameeta Parekh, Team Leader, Ph.D. AP 11/17/98

FT initialed by Ameeta Parekh, Team Leader, Ph.D. /S/ 

cc: NDA 20-582/S-001, HFD (Bennette, Moore), HFD-870 (M.Chen, Parekh, Jarugula), CDR (B.Murphy for Drug).

Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation II

NDA: 20582/S-001
Drug: Follistim™ (follitropin beta for injection)
Sponsor: Organon
Date of Submission: 05/18/98
Type of Submission: Change in diluent
Reviewer: Venkateswar R. Jarugula, Ph.D.

SYNOPSIS

Reference is made to the approved NDA 20-582, for Follistim™, which is indicated for the development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology (ART) program. Sponsor submitted the current supplement to support a change in diluent from 0.45% NaCl to Sterile Water for injection, USP. Sponsor claims that this change is intended to improve the patient comfort during drug administration via subcutaneous or intramuscular injection. The information included in the supplement addresses chemistry requirements and the necessary labeling changes to reflect the change in diluent. However, sponsor did not propose to conduct any *in vivo* bioavailability study or provide any request for waiver for the requirement of a bioavailability study. This submission was discussed internally in DPE II and a concern was raised regarding the effect of change in diluent on systemic availability following subcutaneous or intramuscular injection.

Since the diluent is changed from 0.45% NaCl to sterile water for injection, the composition of the reconstituted solution will be different from the approved. According to CFR 320.21(c), a supplemental application seeking approval for a change in product formulation, should include either

1. Evidence demonstrating the *in vivo* bioavailability of the drug product that is the subject of the application; or
2. Information to permit the FDA to waive the submission of evidence demonstrating *in vivo* bioavailability.

Reviewer Comment:

- Since, the diluent is changed from 0.45% NaCl to water, the composition of the final reconstituted solution will change. The effect of this proposed change on the bioavailability of follitropin is unclear. However, factors such as osmolality and ionic strength may affect bioavailability of a parenteral drug product.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II has reviewed the NDA 20-582/s-001 dated 05/18/98 and recommends the following:

Since the effect of the proposed change in the drug product on its bioavailability is not known, the sponsor should either conduct an in vivo bioavailability study or request a biowaiver by providing scientific rationale for not conducting such a study.

Please convey the Recommendation to the sponsor as appropriate.

/S/

8/24/98

Venkateswar R. Jarugula, Ph.D.

RD initialed by Ameeta Parekh, Acting Team Leader, Ph.D. AP 8/18/98

for FT initialed by Ameeta Parekh, Acting Team Leader, Ph.D.

/S/

8/5/98

cc: NDA 20-582/S-001, HFD (Bennette, Dunson), HFD-870 (M.Chen, Dorantes, Jarugula), CDR (B.Murphy for Drug).