CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
022460Orig1s000

PHARMACOLOGY REVIEW(S)
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 22-460
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: 20 March 09
PRODUCT: [dutasteride/tamsulosin combination product]
INTENDED CLINICAL POPULATION: men with BPH
SPONSOR: GlaxoSmithKline
DOCUMENTS REVIEWED: EDR
REVIEW DIVISION: Division of Reproductive and Urologic Products (HFD-580)
PHARM/TOX REVIEWER: Laurie McLeod-Flynn, Ph.D., D.A.B.T.
PHARM/TOX SUPERVISOR: Lynnda Reid, Ph.D.
DIVISION DIRECTOR: Scott Monroe, M.D.
PROJECT MANAGER: Olga Salis

Date of review submission to Division File System (DFS): 18 November 2009
EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: There is no impediment to approval from a pharmacology/toxicology perspective.

B. Recommendation for nonclinical studies: None at this time.

C. Recommendations on labeling

Proposed labeling: (proposed changes in red and strikethrough)
II. Summary of nonclinical findings

A. Brief overview of nonclinical findings: No new nonclinical toxicology studies were submitted with this application.

B. Pharmacologic activity: Dutasteride is a competitive 5-alpha-reductase antagonist. Tamsulosin, is an alpha-1-adrenoceptor antagonist. A battery of in vitro assays revealed no evidence of overlapping primary or secondary pharmacological activity which would be of concern with regard to this combination of drugs.

C. Nonclinical safety issues relevant to clinical use: No new toxicology studies and no nonclinical studies of this drug combination were submitted. Nonclinical safety issues relevant to clinical use have been previously identified for dutasteride and are adequately described in the previous and proposed labeling i.e. the specific teratogenicity of dutasteride in animal studies at less than clinical exposure levels and the neurotoxicity in animal studies at very high exposures.
2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22460
Review number: 1
Sequence number/date/type of submission: 000 / 20 March 09 / original NDA
Information to sponsor: Yes ( ) No (x)
Sponsor and/or agent: GlaxoSmithKline
Manufacturer for drug substance: GlaxoSmithKline

Reviewer name: Laurie McLeod-Flynn
Division name: Division of Reproductive and Urologic Products
HFD #: 580
Review completion date: 22 October 2009

Drug:
Trade name: [b] Dutasteride and Tamsulosin [b]
Generic name: Dutasteride and Tamsulosin
Chemical name:
Dutasteride: (5α,17β)-N-{2,5 bis(trifluoromethyl) phenyl}-3-oxo-4-azaandrost-1-ene-17-carboxamide
Tamsulosin: R(-)-5-[2-[[2-(2-Ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzene sulfonamide, monohydrochloride
Molecular formula/molecular weight:
Dutasteride: C_{27}H_{30}N_{2}F_{6}O_{2}/ 528.54
Tamsulosin: C_{20}H_{28}N_{2}O_{5}S•HCl/ 444.97

Structure:
Dutasteride:

Tamsulosin:

Relevant INDs/NDAs/DMFs: NDA 21319
Drug class:
  Dutasteride: 5-alpha-reductase antagonist
  Tamsulosin: alpha-1-adrenoceptor antagonist

Intended clinical population: men with BPH

Clinical formulation:

Composition of DTC, 0.5 mg Dutasteride and 0.4 mg Tamsulosin Hydrochloride

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity (per capsule)</th>
<th>Function</th>
<th>Reference to Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dutasteride Product Intermediate</td>
<td>1 each</td>
<td>Active</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>Tamsulosin Hydrochloride Product Intermediate</td>
<td>(b) (4)</td>
<td>Active</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>Pre-printed Hard-Shell Capsule</td>
<td>1 each</td>
<td>Capsule Shell</td>
<td>Supplier</td>
</tr>
</tbody>
</table>

Composition of the Dutasteride Product Intermediate, 0.5 mg

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity (mg/capsule)</th>
<th>Function</th>
<th>Reference to Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fill Solution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dutasteride¹</td>
<td>0.50</td>
<td>Active</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>Mono-di-glycerides of Caprylic/Capric Acid (MDC)¹</td>
<td>(b) (4)</td>
<td></td>
<td>Supplier</td>
</tr>
<tr>
<td>Butylated Hydroxytoluene (BHT)</td>
<td></td>
<td></td>
<td>USNF</td>
</tr>
<tr>
<td>Gelatin</td>
<td></td>
<td></td>
<td>USNF</td>
</tr>
<tr>
<td>Glycerin</td>
<td></td>
<td></td>
<td>USP</td>
</tr>
<tr>
<td>Titanium Dioxide</td>
<td></td>
<td></td>
<td>USNFS</td>
</tr>
<tr>
<td>Ferric Oxide, Yellow²</td>
<td>(b) (4)</td>
<td></td>
<td>Ph.Eur., USNF</td>
</tr>
</tbody>
</table>

Note:
1.  
2. Ferric Oxide is also referred to as Iron Oxide Yellow.
3.  
4.  
## Composition of the Tamsulosin Hydrochloride Product Intermediate, 0.4 mg Tamsulosin Hydrochloride

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity (mg/capsule)</th>
<th>Function</th>
<th>Reference to Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamsulosin Hydrochloride ¹</td>
<td>0.400</td>
<td>Active</td>
<td>Supplier</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>USNF</td>
</tr>
<tr>
<td>Microcrystalline Cellulose</td>
<td></td>
<td></td>
<td>USNF</td>
</tr>
<tr>
<td>Methacrylic Acid Copolymer Dispersion ²</td>
<td></td>
<td></td>
<td>USP</td>
</tr>
<tr>
<td>Talc</td>
<td></td>
<td></td>
<td>USNF</td>
</tr>
<tr>
<td>Triethyl Citrate</td>
<td></td>
<td></td>
<td>USP</td>
</tr>
<tr>
<td>Methacrylic Acid Copolymer Dispersion ²</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Talc</td>
<td></td>
<td></td>
<td>USNF</td>
</tr>
<tr>
<td>Triethyl Citrate</td>
<td></td>
<td></td>
<td>USP</td>
</tr>
<tr>
<td>Note:</td>
<td></td>
<td></td>
<td>-</td>
</tr>
</tbody>
</table>
Composition of the Pre-printed Hard-Shell Capsule, Body and Cap

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity (mg per 100 mg)</th>
<th>Reference to Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrageenan</td>
<td>USNF</td>
<td></td>
</tr>
<tr>
<td>Potassium Chloride</td>
<td>USP</td>
<td></td>
</tr>
<tr>
<td>Titanium Dioxide</td>
<td>USP</td>
<td></td>
</tr>
<tr>
<td>Ferric Oxide, Red</td>
<td>USNF</td>
<td></td>
</tr>
<tr>
<td>FD&amp;C Yellow 6</td>
<td>USP</td>
<td></td>
</tr>
<tr>
<td>Black Ink</td>
<td>Supplier</td>
<td></td>
</tr>
<tr>
<td>Hypromellose</td>
<td>USNF</td>
<td></td>
</tr>
<tr>
<td>Black Ink</td>
<td>USNF</td>
<td></td>
</tr>
</tbody>
</table>

Note:
1. (b) (4) owing to these (b) (4) hard-shell capsules containing propyl par is provided via EMF cap of the capsule body and cap and its ratio is approximately (b) (4) respectively.
2. The amount of ferric oxide (b) (4) does not exceed (b) (4) (b) (4) mg per capsule.
3. The typical amount of black ink (b) (4) is approximately (b) (4) ppm per capsule.
4. The typical amount of black ink (b) (4) is approximately (b) (4) ppm per capsule.

Route of administration: oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance: Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 22460 are owned by GlaxoSmithKline or are data for which GlaxoSmithKline has obtained a written right of reference. Any information or data necessary for approval of NDA 22460 that GlaxoSmithKline does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug’s approved labeling. Any data or information described or referenced below from a previously approved application that GlaxoSmithKline does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22460.

Studies reviewed within this submission:

An in vitro preclinical profile of GI138525A (Tamsulosin) at a range of 7-transmembrane Receptors (Glaxo, 2007).

The preclinical in vitro profile of GI138525A (Tamsulosin) at a selection of 7 transmembrane monoamine receptors (Glaxo, 2006).

Tamsulosin (GI138525A) has low affinity for the human hERG channel (Glaxo, 2007).
PHARMACOLOGY

Study title: The preclinical in vitro profile of GI138525A (Tamsulosin) at a selection of 7 transmembrane monoamine receptors (Glaxo, 2006).

In agreement with published literature, GI138525A had high affinity and profiled as an antagonist at the alpha1A and alpha1B adrenoreceptors with fpKi's of ~10.3 and 9.8, respectively.

GI138525A was inactive in these agonist assays: A2a pEC50 <4.5, A2b pEC50 <4.5.

GI138525A was inactive in these antagonist assays: A2b pKi <5.2, EP3 pKi <5.2, H3 fpKi <6.2.

GI138525A was active in these agonist assays; D2 short pEC50 8.2, D4 pEC50 7.5, 5-HT1A pEC50 8.6, 5-HT1B pEC50 6.5.

GI138525A was active in these antagonist assays: D2 long fpKi 7.8, D3 fpKi 8.7, D4 fpKi 7.4, H1 fpKi range 5.3-6.0 for two technologies.

These results indicate that GI138525A has measurable activity at a range of receptors with the following fold selectivity when compared to the primary alpha 1A adrenoreceptor antagonist data.

Less than 10 fold- alpha 1B (ant)
Between 10 and 100 fold - 5-HT1A (ag), D3 (ant)
Greater than 100 fold - Adenosine A2a (ag), Adenosine A2b (ag/ant), Dopamine D2 (ag (S)/ant (L)), D4 (ag/ant), EP4 (ant), 5-HT1B (ag), histamine H1 (ant), H3 (ant).

Study title: An in vitro preclinical profile of GI138525A (Tamsulosin) at a range of 7-transmembrane receptors (Glaxo, 2007).

GI138525A had high affinity at the human alpha1A, alpha1B and alpha1D adrenoreceptors with pKi’s of ~10.2, 9.2 and 9.8, respectively.

GI138525A was inactive in these human receptor binding assays: alpha2C pIC50 <4.8, CCR5 pIC50 <4.5, galanin pIC50 <4.4, glucagon pIC50 <4.5, NPY1 pIC50 <4.5, NPY2 pIC50 <4.5, NPY4 pIC50 <4.5, NPY5 pIC50 <4.5, orexin1 pIC50 <4.5.


GI138525A was inactive in an antagonist assay at the following human receptor: MCH
pIC$_{50} < 4.5$.

GI138525A was inactive in the following animal orthologue agonist assays: hamster CT2 pEC$_{50} < 4.5$ and against frog melanophore endogenous receptors coupled via Gi, Go or Gs all pEC$_{50} < 4.5$.

GI138525A was inactive in the following animal orthologue antagonist assay: hamster thrombin pIC$_{50} < 4.5$.

GI138525A was active in these binding assays: alpha$_2$A pEC$_{50}$ 6.4, alpha 2B pEC$_{50}$ 6.4.

These results indicate that GI138525A has measurable activity at some of the range of human receptors tested with the following fold selectivity when compared to the primary alpha 1 A adrenoreceptor binding data.

Less than 10 fold - alpha1D  
Between 10 and 100 fold - alpha1B  
Nearly 6000 fold - alpha2A and alpha2B  
Greater than 10000 fold - alpha2C (binding), CCR5 (binding), galanin (binding), glucagons (binding), NPY1 (binding), NPY2 (binding), NPY 4 (binding), NPY5 (binding), orexin1 (binding), betal (agonist), beta2 (agonist), beta3 (agonist), CT2 (agonist), EP2 (agonist), GLPl (agonist), MC1 (agonist), MC3 (agonist), MC4 (agonist), MC5 (agonist), PTH1 (agonist), CCR3 (agonist), orexin2 (agonist), MCH (agonist).

**Safety pharmacology**

**Study title: Tamsulosin (GI138525A) has low affinity for the human hERG channel (Glaxo, 2007).**

Tamsulosin (GI138525A) was tested in a binding assay at the human hERG ion channel. The compound displaced the radioligand ([³H]-dofetilide) at pIC$_{50}$ 4.8±0.2 (n=64). The asymptote of the curve fit was 99±7%, consistent with complete displacement.

Tamsulosin was also tested in an FP binding assay (n=2) with a pIC$_{50}$ of 4.6.

**Conclusion:** A battery of *in vitro* assays revealed no evidence of overlapping primary or secondary pharmacological activity which would be of concern with regard to this combination of drugs.
<table>
<thead>
<tr>
<th>Application Type/Number</th>
<th>Submission Type/Number</th>
<th>Submitter Name</th>
<th>Product Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA-22460</td>
<td>ORIG-1</td>
<td>SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLINE</td>
<td>DUTASTERIDE/ TAMSULOSIN HYDROCHLORIDE</td>
</tr>
</tbody>
</table>

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Laurie L McLeod Flynn
11/18/2009

Lynnda L Reid
11/18/2009

I concur with Dr. McLeod-Flynn's review of NDA 22-460:
- there are no outstanding safety issues with this combination product
- proposed draft labeling

Nonclinical data support approval.