**ABSTRACT**

5-alpha reductase is an important enzyme in metabolic pathway of testosterone. Its three subtypes SRD5A1, SRD5A2 and SRD5A3 are responsible for conversion of testosterone to its more potent derivative dihydrotestosterone (DHT). Excess production of DHT leads to prostate cancer and alopecia. The production of DTH can be reduced by inhibiting the 5-alpha reductase enzyme. Several 5-alpha reductase inhibitors were synthesized in the past and are marketed and used for the treatment of prostate cancer and baldness. The dosing of these drugs is between 1 to 5 mg/day. The low dosing of these drugs need special attention on quality control and quantitative estimation of drug in formulation and biological fluids. The details of 5-alpha reductase inhibitors and the recent developments in their quantitative estimation have been compiled in the presented review.

**KEYWORDS:** 5-α-reductae inhibitors, cancer, quantitative estimation.

**1. INTRODUCTION**

**1. 5-α-Reductase**

1.1. 5-α-reductases, also known as 3-oxo-5α-steroid 4-dehydrogenases, are enzymes involved in steroid metabolism. They participate in 3 metabolic pathways: bile acid biosynthesis, androgen and estrogen metabolism. There are three isoenzymes of 5-alpha reductase, which vary in different tissues with age.

1.2. The three isoenzymes of 5-alpha reductase are: steroid 5-α-reductase 1, 2, and 3 (SRD5A1, SRD5A2 and SRD5A3). 5-α-reductase is known for converting testosterone, the male sex hormone, into the more potent dihydrotestosterone.
1.3. 5α-reductase 1 is present in most tissues in the body where 5α-reductase is expressed, and is the dominant form in sebaceous glands. 5α-reductase 2 is the dominant isoenzyme in genital tissues, including the prostate. While the 5αs-reductase 3 is expressed in liver.

1.4. 5α-reductase has greater affinity for androgen receptors. The activity of 5α-reductase inhibitors results in increased levels of testosterone and decreased levels of dihydrotestosterone.

1.5. **5α-reductase inhibitors**[^4]: The 5α-reductase inhibitors have androgenic effects and used primarily in the treatment of benign prostatic hyperplasia (BPH) and alopecia. These agents inhibit the enzyme 5α-reductase that prevents conversion of testosterone, to the more potent DHT.

1.6 The drugs in this class shown in fig.1 includes Alfatradiol (1); Bexlosteride (2); Dutasteride (3); Episteride (4); Finasteride (5); Izonsteride (6); Turosteride (7); Lapisteride (8).

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2. Alfatradiol[^5,6,7]
Alfatradiol or 17α-estradiol is a 5α-reductase inhibitor used topically for the treatment of androgenic alopecia (hair loss) in men and women.

2.1 IUPAC name
Estra-1,3,5(10)-triene-3,17α-diol.

2.2 Marketed preparations
It is marketed under the name of pantostin, Avicis, Avixis and Ell-Cranell.

2.3. Mechanism of action
Alfatradiol acts as an inhibitor of the enzyme 5-α-reductase, which is responsible for the activation of testosterone to dihydrotestosterone, and which plays a role in regulating hair growth.

2.4. Side effects
Alfatradiol cause Dizziness, Headache, Nausea, Oedema (fluid retention), and Increase in weight, Skin pigmentation.

2.5. Contraindications
It is not used in pregnancy or lactation condition and not to be used by patient who are less than 18 years of age.

2.6. Dose
Recommended dose of alfatradiol is 0.025% in 100 ml is given once daily.

3. Bexlosteride[^8,9,10]
Bexlosteride (LY-191,704) is a potent and noncompetitive inhibitor of the enzyme 5α-reductase related to finasteride and dutasteride. It is selective for the type I isoform of the enzyme. It was never marketed.

3.1. IUPAC name
(4αS,10bR)-8-chloro-4-methyl-1,2,4a,5,6,10b-hexahydrobenzo[f]quinolin.

3.2. Marketed preparations
It was never marketed.
3.3. Mechanism of action
Bexlosteride is antiandrogenic as they prevent the conversion of testosterone to dihydrotestosterone (DHT). DHT is 3-5 times more potent than testosterone or other androgens (except in skeletal muscle tissue, where testosterone is the main androgen). They are unique because they do not counteract the effects or production of other androgens other than DHT. Dihydrotestosterone is necessary for development of both external male sex organs and the prostate.

3.4. Side effects
Bexlosteride cause side effects such as decreased libido, decreased ejaculate volume, depression, and anxiety. Rare ADRs include breast tenderness and enlargement (gynecomastia), and allergic reaction.

4. Dutasteride\[11, 12, 13]\nDutasteride is 5-\(\alpha\)-reductase inhibitor that inhibits conversion of testosterone to dihydrotestosterone (DHT). It is used to treat benign prostatic hyperplasia.

4.1. IUPAC name
\((5\alpha,17\beta)-N\{2, 5-Bis(trifluoromethyl)phenyl\}-3-oxo-4-azaandrost-1-ene-17-carboxamide\).

4.2. Marketed preparation
Marketed preparations are Avodart (soft gelatin capsule manufactured by galaxosmith).

4.3. Mechanism of action
Dutasteride inhibits the conversion of testosterone to dihydrotestosterone (DHT). DHT is primarily responsible for the initial development and subsequent enlargement of the prostate gland. Testosterone is converted to DHT by the enzyme known as 5-\(\alpha\)-reductase, which exists as 3 isoforms, type 1 and type 2 and type 3.

Dutasteride is an inhibitor of type 1 and type 2 of 5-\(\alpha\)-reductase isoenzymes, with which it forms a stable enzyme complex. Dissociation from this complex has been evaluated under \textit{in vitro} and \textit{in vivo} conditions and is extremely slow. Dutasteride does not bind to the human androgen receptor.
4.4. Side effects
Less serious side effects may include:

- Decreased libido (sex drive);
- Decreased amount of semen released during sex;
- Impotence (trouble getting or keeping an erection); or
- Breast enlargement.

4.5. Contraindication

**Dutasteride (Avodart) is contraindicated for use in**

- Pregnancy: In animal reproduction and developmental toxicity studies, dutasteride inhibited development of male fetus external genitalia. Therefore, Avodart may cause fetal harm when administered to a pregnant woman. If dutasteride is used during pregnancy or if the patient becomes pregnant while taking Avodart, the patient should be apprised of the potential hazard to the fetus.
- Women of childbearing potential
- Pediatric patients
- Patients with previously demonstrated, clinically significant hypersensitivity (e.g., serious skin reactions, angioedema) to Avodart or other 5 alpha-reductase inhibitors.

4.6. Dose

The recommended dose of AVODART (Dutasteride) is 1 capsule (0.5 mg) taken once daily.

5. Episteride\(^{14, 15, 16}\)

Episteride is a non-competitive inhibitor of the type II isoform of the enzyme \(5\alpha\)-reductase, similarly to finasteride and turosteride. It was under development for the treatment of benign prostatic hyperplasia and acne vulgaris. But it was never marketed.

5.1. IUPAC name

17-(\(\text{tert}\)-butylcarbamoyl)androsta-3,5-diene-3-carboxylic acid.

5.2. Marketed preparation

It was never marketed.

5.3. Mechanism of action

The mechanism of episteride in the treatment of benign prostatic hyperplasia might be apoptosis stimulated by decreasing dihydrotestosterone level.
5.4. Side effects
It may cause depression and many acne problems.

6. Finasteride\textsuperscript{[17, 18, 19]}
Finasteride is a drug used for the treatment of benign prostatic hyperplasia (BPH) and male pattern baldness (MPB).

6.1. IUPAC name
$N$-(1,1-dimethylethyl)-3-oxo-(5α,17β)-4-azaandrosten-1-ene-17-carboxamide.

6.2. Marketed preparation
Finasteride cause proscar, propecia.

6.3. Mechanism of action
Finasteride is a 5-α-reductase inhibitor, specifically the type II and III isoenzymes. By inhibiting 5α-reductase, finasteride prevents conversion of testosterone to dihydrotestosterone (DHT) by the type II and III isoenzymes, resulting in a decrease in serum DHT levels. By blocking DHT production, finasteride reduces androgen activity in the scalp. In the prostate, inhibition of 5-α-reductase reduces prostate volume, which improves BPH and reduces risk of prostate cancer.

6.4. Side effects
It can cause hair loss (androgenic alopecia) sand allergic reaction.

6.5. Contraindication
Finasteride is not approved for use in women, especially due to risks of birth defects in a fetus.

6.6. Dose
The recommended dose of propecia is 1 tablet (1 mg) taken once daily. And dose for proscar is 1 tablet (5mg) taken once daily.

7. Izonsteride\textsuperscript{[20]}
Izonsteride is useful in the treatment of androgenic alopecia.
7.1. IUPAC name
(4aR,10bR)-8-[(4-ethyl-1,3-benzothiazol-2-yl)sulfanyl]-4,10b-dimethyl-1,4,4a,5,6,10b-hexahydrobenzo[f]quinolin-3(2H)-one.

7.2. Marketed preparation
It is never marketed.

7.3. Mechanism of action
It is a selective inhibitor of the 5-α-reductase, with dual effects on both the type I and type II isoforms of the enzyme. It was used for the treatment of benign prostatic hyperplasia but was never marketed. Izonsteride may also be useful in the treatment of androgenic alopecia.

7.4. Side effects
It can cause anxiety, depression.

7.5. Contraindication
It is not approved for use in women, especially due to risks of birth defects in a fetus.

8. Lapisteride\cite{21, 22}
Lapisteride is a dual inhibitor of both isoforms of the enzyme 5-α-reductase. It was under investigation for the treatment of benign prostatic hyperplasia (BPH) and androgenic alopecia, but was never marketed.

8.1. IUPAC name
N-[1-(4-methoxyphenyl)-1-methylethyl]-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide.

8.2. Marketed preparation
It was never marketed.

8.3. Mechanism of action
It is a dual inhibitor of both isoforms of the enzyme 5-α-reductase. It was under investigation for the treatment of benign prostatic hyperplasia (BPH) and androgenic alopecia. But was never marketed.

8.4. Side effects
This drug causes depression, and anxiety. Rare ADRs include breast tenderness and enlargement (gynecomastia), and allergic reaction.
Turosteride\textsuperscript{[23,24,25]}

Turosteride (FCE-26,073) is a selective inhibitor of the enzyme 5-α-reductase. It is useful for the treatment of acne, hair loss and mainly for androgenic alopecia.

9.1. IUPAC name

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(4aR,4bS,6aS,7S,9aS,9bS,11aR)-1,4a,6a-trimethyl-2-oxo-N-(propan-2-yl)-N-(propan-2-ylcarbamoyl)hexadecahydro-1H-indeno[5,4-f]quinoline-7-carboxamide.
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9.2. Marketed preparation

It was never marketed.

9.3. Mechanism of action

It is a selective inhibitor of the enzyme 5-α-reductase which was under investigation for the treatment of benign prostatic hyperplasia (BPH), but was never marketed. Similarly to finasteride, turosteride is selective for the type II isoform of 5α-reductase, with about 15-fold selectivity for it over type I isoform of the enzyme. In animal studies it has been shown to inhibit prostate size and retard tumor growth.

9.4. Side effects

Turosteride cause the side effects such as gynecomastia, erectile dysfunction and depression.

REFERENCES


11. Yamana K, Labrie F. Human type 3 5-α-reductase is expressed in peripheral tissues at higher levels than types 1 and 2 and its activity is potently inhibited by finasteride and dutasteride. Hormone Molecular Biology and Clinical Investigation, 2010; 2(3): 293–299.


