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Ezetimibe (Zetia®): A Novel Lipid-Lowering Agent

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Introduction

Hypercholesterolemia involves the existence of large quantities of cholesterol in the cells and blood plasma. It is caused by a disturbance in the lipid transport process that results from increased lipoprotein synthesis or decreased lipoprotein degradation. These lipoproteins are responsible for transporting cholesterol and triglycerides (TG) in the plasma. The two major classes of lipoproteins are low-density lipoproteins (LDL) and high-density lipoproteins (HDL). An estimated 100 million adults in the United States have total-cholesterol levels above normal (= 200mg/dL).[1] Of those, 40 million have levels that are = 240mg/dL.[1] Reduction of LDL cholesterol is a key approach for lowering the risk of coronary heart disease (CHD), resulting in reduced cardiovascular morbidity and mortality.[2] The FDA approved Zetia® (ezetimibe) in October 2002 as a new oral treatment for hypercholesterolemia. Merck/Schering-Plough Pharmaceuticals are marketing the drug in the United States.

Ezetimibe is a novel selective inhibitor of intestinal cholesterol absorption from dietary and biliary sources without affecting the absorption of fat soluble vitamins and triglycerides.[3, 4] Ezetimibe alone is indicated as adjunctive therapy to diet and exercise for the reduction of total cholesterol (Total-C), LDL, and apolipoprotein B (Apo B) in patients with primary hypercholesterolemia and the reduction of elevated sitosterol and campesterol levels in patients with homozygous sitosterolemia. It is also indicated in combination with an HMG-CoA reductase inhibitor for the reduction of elevated total-C, LDL, and ApoB in patients with primary hypercholesterolemia and homozygous familial hypercholesterolemia. This article will discuss the pharmacology, pharmacokinetics, clinical trials, adverse effects, and cost of ezetimibe.

Pharmacology

Ezetimibe decreases blood cholesterol by inhibiting the absorption of cholesterol by the small intestine. Unlike other cholesterol-lowering compounds, ezetimibe does not inhibit cholesterol synthesis in the liver nor does it increase bile acid excretion. Ezetimibe acts at the brush border of the small intestine to inhibit the absorption of cholesterol leading to a reduction in the amount of cholesterol delivered to the liver. This in turn causes a reduction of hepatic cholesterol stores and an increase in cholesterol clearance from the blood which makes ezetimibe use an appropriate adjunct to HMG-Co A reductase inhibitors.

Pharmacokinetics

Ezetimibe is available as 10mg tablets. The recommended dose of ezetimibe is 10mg once daily without regard to meals for all its approved indications. Within 4-12 hours of the oral administration of a 10mg dose to fasting adults, the attained mean ezetimibe peak plasma concentration (Cmax) was 3.4–5.5 ng/ml.[5] Following oral administration, ezetimibe is absorbed and extensively conjugated to a phenolic glucuronide (active metabolite). Mean Cmax (45—71 ng/ml) of ezetimibe-glucuronide are attained within 1—2 hours.[5] The concomitant administration of food (high-fat vs. non-fat meals)

Table 1. Response to ezetimibe in patients with primary hypercholesterolemia after 12 weeks (mean[a] % change from untreated baseline[b])[5]

Study	Treatment Group	N	Total-C	LDL	ApoB	TG[a]	HDL
Study 1[c]	Placebo	205	+1	+1	-1	-1	-1
	Ezetimibe 10mg	622	-12	-18	-15	-7	+1
Study 2[c]	Placebo	226	+1	+1	-1	+2	-2
	Ezetimibe 10mg	666	-12	-18	-16	-9	+1
Pooled data[c]	Placebo	431	0	+1	-2	0	-2
	Ezetimibe 10mg	1288	-13	-18	-16	-8	+1

N=number of subjects, Total-C=total cholesterol, LDL=low density lipoproteins, Apo B=apolipoprotein B, TG=triglycerides, HDL=high density lipoproteins
[a]median % change from baseline; [b]baseline (on no lipid-lowering drug), [c]Ezetimibe significantly reduced Total-C, LDL, Apo B, and TG, and increased HDL compared to placebo.

has no effect on the extent of absorption of ezetimibe. However, co-administration with a high-fat meal increases the Cmax of ezetimibe by 38%.[5] The absolute bioavailability cannot be determined since ezetimibe is insoluble in aqueous media suitable for injection. Ezetimibe and its active metabolite are highly bound to human plasma proteins (90%).[5]

Ezetimibe is primarily metabolized in the liver and the small intestine via glucuronide conjugation with subsequent renal and biliary excretion. Both the parent compound and its active metabolite are eliminated from plasma with a half-life of approximately 22 hours allowing for once daily dosing. Ezetimibe lacks significant inhibitor or inducer effects on cytochrome P-450 isoenzymes which explains its limited number of drug interactions (Table 4). No dose adjustment is needed in patients with renal insufficiency or mild hepatic dysfunction (Child-Pugh score 5-6). Due to insufficient data, the manufacturer does not recommend ezetimibe for patients with moderate to severe hepatic impairment (Child-Pugh score 7-15). In patients with mild, moderate, or severe hepatic impairment, the mean AUC values for total ezetimibe are increased approximately 1.7-fold, 3-4 fold, and 5-6 fold respectively, compared to healthy subjects.[5]

Clinical Trials

Ezetimibe Monotherapy

In two multicenter, double blinded, placebo-controlled 12 week studies that compared ezetimibe monotherapy with placebo in 1719 patients with primary hypercholesterolemia, ezetimibe significantly lowered total-C, LDL, Apo B, and TG, and increased HDL compared to placebo (Table 1).[5]

Add-on to Statin

In a multicenter, double-blinded, placebo-controlled 8 week study, 769 patients with primary hypercholesterolemia, CHD, or multiple cardiovascular risk factors who were receiving a statin but had not met their NCEP ATP III LDL goal were randomized to receive either ezetimibe or placebo in addition to their on-going statin therapy. Ezetimibe, added to on-going statin therapy, sig-

Table 2. Response to the addition of ezetimibe to on-going statin therapy[a] in patients with hypercholesterolemia after 8 weeks (mean[b] % change from treated baseline[c])[6]

Treatment (Daily Dose)	N	Total-C	LDL	Apo B	TG	HDL
On-going statin + Placebo[d]	390	-2	-4	-3	-3	+1
On-going statin + Ezetimibe10mg[d]	379	-17	-25	-19	-14	+3

N=number of subjects, Total-C=total cholesterol, LDL=low density lipoproteins, Apo B=apolipoprotein B, TG=triglycerides, HDL=high density lipoproteins
[a]patients receiving each statin: 40% atorvastatin, 31% simvastatin, 29% others (pravastatin, fluvastatin, cerivastatin, lovastatin); [b]median % change from baseline; [c]baseline (on a statin alone); [d]ezetimibe 10mg + statin significantly reduced Total-C, LDL, Apo B, and TG, and increased HDL compared to statin alone.

Table 3. Response to ezetimibe and simvastatin initiated at the same time in patients with primary hypercholesterolemia (mean[a] % change from untreated baseline[b])[7]

Treatment (Daily Dose)	N	Total-C	LDL	Apo B	TG[a]	HDL
Placebo	70	-1	-1	0	+2	+1
Ezetimibe	61	-13	-19	-14	-11	+5
Simvastatin 10mg	70	-18	-27	-21	-14	+8
Ezetimibe + Simvastatin 10mg	67	-32	-46	-35	-26	+9
Simvastatin 20mg	61	-26	-36	-29	-18	+6
Ezetimibe + Simvastatin 20mg	69	-33	-46	-36	-25	+9
Simvastatin 40mg	65	-27	-38	-32	-24	+6
Ezetimibe + Simvastatin 40mg	73	-40	-56	-45	-32	+11
Simvastatin 80mg	67	-32	-45	-37	-23	+8
Ezetimibe + Simvastatin 80mg	65	-41	-58	-47	-31	+8
Pooled Data (Simvastatin)[c]	263	-26	-36	-30	-20	+7
Pooled Data (Ezetrimibe + Simvastatin)[c]	274	-37	-51	-41	-29	+9

N=number of subjects, Total-C=total cholesterol, LDL=low density lipoproteins, Apo B=apolipoprotein B, TG=triglycerides, HDL=high density lipoproteins
[a]median % change from baseline, [b]baseline (on no lipid-lowering drug), [c]Ezetimibe 10mg + all doses of simvastatin pooled (10-80mg) significantly reduced Total-C, LDL, Apo B, and TG, and increased HDL compared to all doses of simvastatin pooled (10-80mg).

nificantly lowered total-C, LDL, Apo B, and TG, and increased HDL compared with the statin administered alone (Table 2).[6] In addition, the investigators concluded that LDL reductions with ezetimibe were generally consistent across all statins.

Coadministration with Statin

In a multicenter, double-blinded, placebo-controlled 12 week trial in 668 hypercholesterolemic patients, ezetimibe 10mg alone or placebo was initiated at the same time with simvastatin 10mg-80mg. Ezetimibe significantly lowered total-C, LDL, Apo B, and TG, and increased HDL compared with simvastatin administered alone (Table 3).[7] In three other similar multicenter, double blinded, placebo-controlled 12 week trials in hypercholesterolemic patients that compared the benefits of ezetimibe initiated concurrently with atorvastatin, pravastatin, and lovastatin, ezetimibe significantly lowered total-C, LDL, Apo B, and TG, and with the exception of pravastatin increased HDL compared to the statin administered alone.[5]

In a double-blinded, randomized, 12 week study, 50 patients with homozygous familial hypercholesterolemia already receiving atorvastatin or simvastatin were randomized to one of three treatment groups; atorvastatin or simvastatin (80mg), ezetimibe administered with atorvastatin or simvastatin (40mg), or ezetimibe administered with atorvastatin or simvastatin (80mg). Ezetimibe administered with atorvastatin or simvastatin (40 and 80mg pooled statins groups), significantly reduced LDL (20.7%) compared with increasing the dose of atorvastatin or simvastatin monotherapy from 40 to 80mg (7%).[8] In the subgroup of patients who where treated with ezetimibe plus 80mg atorvastatin or simvastatin, LDL was reduced by 27.5%.[8]

Adverse Effects

Ezetimibe's safety has been evaluated in more than 4700 patients.[5] Clinical studies have demonstrated that ezetimibe is generally well tolerated when administered alone or in combination with a statin.[5] When compared to placebo, the overall incidence of adverse effects was similar. Likewise, the discontinuation rate due to adverse effects was similar to placebo.[5] In general, adverse effects were similar between ezetimibe administered with statins and statins alone. However, the frequency of increased transaminases was slightly higher in patients receiving ezetimibe in combination with stat-

Table 4. Potential Drug-Drug Interactions with ezetimibe[5,9]

Drug	Effect
Antacids	Administering ezetimibe with antacids has no significant effect on the AUC of ezetimibe or its active metabolite. However, the peak plasma concentration of ezetimibe is decreased by 30%. To minimize this interaction, it is recommended that ezetimibe be administered 2 hrs before or 4 hrs after the administration of antacids.
Cholestyramine	Mean AUC of ezetimibe was decreased approximately 55% when it was administered concomitantly with cholestyramine. To minimize this interaction, ezetimibe should be administered 2 hrs before or 4 hrs after the administration of cholestyramine. A similar effect might be expected to occur with the concomitant administration of colestipol or colesevelam with ezetimibe; however, this potential interaction has not been studied.
Colesevelam	Similar effect as cholestyramine is expected; however, this potential interaction has not been studied.
Colestipol	Similar effect as cholestyramine is expected; however, this potential interaction has not been studied.
Cyclosporine	Ezetimibe levels were increased 12 fold in one renal transplant patient receiving multiple medications including cyclosporine.
Fibrates	Fibrates can increase cholesterol excretion into the bile which in turn has the potential to promote cholelithiasis. In pre-clinical trials, ezetimibe was reported to increase cholesterol in gallbladder bile in dogs. Theoretically this would increase the risk of having cholelithiasis; therefore, the manufacturer does not recommend the use of ezetimibe in patients receiving fibrates.
Fenofibrate	Concomitant administration with ezetimibe resulted in 1.5 fold increase in total ezetimibe concentrations.
Gemfibrozil	Concomitant administration with ezetimibe resulted in 1.7 fold increase in total ezetimibe concentrations.

*This list is not all inclusive as it is based on findings in pre-clinical trials. More drug-drug interactions may evolve as ezetimibe is used in clinical practice.

ins than in patients receiving statins alone.[5] Due to this unexplained transient increase in liver enzymes, the manufacturer does not recommend the use of ezetimibe in patients with moderate or severe hepatic dysfunction. When used in patients with mild hepatic dysfunction, close monitoring is recommended.

Drug Interactions

Ezetimibe lacks significant inhibitor or inducer effects on cytochrome P-450 isoenzymes. Potential drug-drug interactions are listed in Table 4.

Cost

The cost of a 30-day supply of Zetia® 10mg ranges from $50-60 per month.[9]

Summary

Ezetimibe, used alone or in combination with statins, positively affects the lipid profile of patients with hypercholesterolemia by primarily decreasing LDL cholesterol. Ezetimibe's tolerability and effectiveness has been demonstrated in multiple clinical trials. Co-administration of ezetimibe with statins offers a new approach to further reduce LDL cholesterol while avoiding high doses of statins, thus allowing more patients to reach their treatment goals in a safe and effective manner.

References

1. American Heart Association. 2001 Heart and Stroke Statistical Update. Dallas, Texas: American Heart Association; 2000.
2. Executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA 2001;285:2486-2497.
3. Van Heek M, France CF, Compton DS, et al. In vivo metabolism-based discovery of a potent cholesterol absorption inhibitor, SCH58235, in the rat and rhesus monkey through the identification of the active metabolites of SCH48461. J Pharmacol Exp Ther 1997;283: 157-163.
4. Knopp RH, Bays H, Manion CV, et al. Effect of ezetimibe on serum concentrations of lipid-soluble vitamins (abstract) Atherosclerosis 2001;2 (suppl):90.
5. Zetia® Product Information. Merck/Schering-Plough Pharmaceuticals, 2002.
6. Gagne C, Bays HE, Stuart R, et al. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. Am J Cardiol 2002;90:1084-1091.
7. Davidson MH, et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. J Am Coll Cardiol 2002;40:2125-2134.
8. Gagne C, Gaudet D, Bruckert E, et al. Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia. Circulation 2002;105:2469-2475.
9. Zetia® Drug Monograph. Clinical Pharmacology Online 2003 January. Gold Standard Media. Available from: URL: http://cpip.gsm.com.

DUTASTERIDE (AVODART™): A NEW 5a-REDUCTASE INHIBITOR

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Introduction

Benign Prostatic Hypertrophy (BPH) is the most common cause of voiding dysfunction in men. The disorder affects men over the age of 45 and increases in frequency with age so that by the eighth decade of life more than 90% of men have prostatic hypertrophy at autopsy.[1,2] BPH is a heterogeneous disease, which may be asymptomatic but often becomes symptomatic from the fifth decade of life. Obstructive symptoms of the disease include weak urinary stream/dribbling, urinary hesitancy and sensation of incomplete voiding; irritative symptoms include urinary frequency, urgency and nocturia. Medical and/or surgical treatment is indicated when symptoms interfere with quality of life.[3]

The development of BPH requires a combination of testicular androgens and the ageing process. Although the role of androgens as a causative factor for BPH is debated, they undoubtedly play, at least, a permissive role.[4] Dihydrotestosterone (DHT) is the primary androgen responsible for prostatic enlargement and bladder outlet obstruction, and contributes to the progressive nature of the disease. It is generated by the reduction of testosterone, a process that utilizes two isoenzymes of 5α-reductase. Although not elevated in BPH, DHT levels in the prostate remain at normal levels despite decreasing levels of testosterone that occur with age.

Several forms of medical or surgical treatments are available for men with advanced symptoms. Treatment with luteinizing hormone-releasing hormone (LHRH) analogues or 5a-reductase inhibitors shrinks prostatic hyperplastic cells by lowering tissue DHT levels.

Dutasteride, which is manufactured by GlaxoSmithKline, is the newest addition to the 5α-reductase class. It was approved by the FDA on November 20, 2001 for the treatment of lower urinary tract symptoms (LUTS) due to enlarged prostate and BPH.

This article will review pertinent pharmacology, pharmacokinetics, clinical trials, adverse drug reactions, drug interactions, dosage, and economic issues related to dutasteride.

Pharmacology/Pharmacokinetics

Durasteride is a competitive and specific inhibitor of both type 1 and type 2 5α-reductase isoenzymes. Both isoenzymes are involved in the conversion of testosterone to 5α-DHT, the primary androgen that stimulates the development and subsequent enlargement of the prostate gland. Type 2 isoenzyme is primarily active in the reproductive organs (prostate, seminal vesicles, epididymides) and is responsible for two-thirds of circulating DHT. Type 1 isoenzyme is mostly active in the liver and the skin. Compared to finasteride, which inhibits mostly the type 2-isoenzyme, dutasteride inhibits type 1 isoform as well, reducing DHT formation in the skin and liver. Studies with finasteride have shown that the drug reduces circulating levels of DHT by 60-80% from baseline while dutasteride reduced the levels by more than 90%[5,6] This higher potency is due to dual inhibition of 5α -reductase enzymes. In addition dutasteride reduced the mean prostate volume by a mean of 25.7% at 24 months and BPH related surgical intervention by 48% compared to placebo.

Following oral administration of a single 0.5 mg dose, the time to peak serum concentration (T_{max}) occurred within 2-3 hours.[7] The absolute oral bioavailability in healthy subjects is approximately 60% (range 40%-90%). When the drug is administered with food, the maximum serum concentrations were reduced by 10%-15%, however this reduction is of no clinical significance. Dutasteride is highly bound (99%) to plasma albumin and alpha-1 glycoprotein. Pharmacokinetic data shows that the drug has a large volume of distribution (300-500L). Similar to plasma, steady state concentrations in semen were achieved six months after continuous administration of the drug.

Dutasteride is extensively metabolized by the CYP3A4 isoenzyme to three major and two minor metabolites. Only one of the major metabolites, 6β-hydroxydutasteride has pharmacological activity comparable to that of the parent drug. The drug

Table 1. Changes in primary and secondary endpoints: placebo vs. dutasteride[6]

Parameter (units)	Time (months)	Placebo (mean ± SD)	Dutasteride (mean ± SD)	Group Comparison (*p*-value)
Serum DHT (pg/ml)	24	16 ± 150	-389 ± 228	<0.001
Serum Testosterone (pg/ml)	24	36 ± 1226	749 ± 1475	<0.001
TPV (cm^3)	24	0.8 ± 14.3	-14.6 ± 13.5	<0.001
AUA-SI	24	-2.3 ± 6.8	-4.4 ± 6.6	<0.001
Q_{max} (ml/s)	24	0.6 ± 4.7	2.2 ± 5.2	<0.001
Serum PSA (ng/ml)	24	0.5 ± 2.1	-2.2 ± 2.0	<0.001

DHT=dihydrotestosterone, TPV=total prostate volume, Q_{max}=maximal flow rate, AUA-SI=American Urological AssociationSymptom Index, PSA=prostate specific antigen.

and its metabolites were excreted mainly in the feces, with 5% as unchanged drug and 40% metabolites. The terminal elimination half-life at steady state is approximately 5 weeks, and serum concentrations of the drug remain detectable for 4-6 months after treatment is stopped.[8] It is believed that the increased DHT lowering effect of dutasteride is not only due to its greater inherent potency, but also its long terminal half-life.[9]

Clinical Trials

A limited number of trials are available which evaluate the efficacy, safety and tolerability of dutasteride. To date, the safety and efficacy of the drug has been reported on the basis of three pooled 2-year Phase III clinical trials.

GG Roehrborn et al. summarized and presented the data from the three trials. A total of 4325 men aged 50 years and over with clinical benign prostatic hyperplasia and moderate to severe symptoms were enrolled in three identical trials and randomized to dutasteride 0.5 mg or matching placebo. After 1 month of a single-blind placebo-run-in period, patients were followed for 24 months in a double-blinded fashion with assessments done at multiple intervals. The primary endpoints were changes in American Urological Association-Symptom Index (AUA-SI) and risk of Acute Urinary Retention (AUR). Secondary endpoints included: changes in total prostate volume (TPV), maximal flow rate (Q_{max}), surgical intervention, serum prostate specific antigen (PSA), serum testosterone, serum DHT, and safety and tolerability of the drugs. In all the studies, the assessment was done at 1, 3, 6, 12, 18, and 24 months for AUA-SI, $Q_{max,}$ and PSA and at 12 and 24 months for testosterone and DHT. The TPV was measured at 1, 3, 6, 12, and 24 months. Out of the 4325 men who were randomized, 2951 men (68%) completed the 24-month follow-up period. The dropout rate for the dutasteride group and placebo was 30.32% and 33.32% respectively. Reasons for discontinuation included lack of efficacy (25.18%), adverse event (28.02%), loss of follow-up (8.66%) and consent withdrawal (19.21%). However, the only reason for discontinuation that reached statistical significance between the dutasteride and placebo-treated groups was lack of efficacy, 20.39% versus 29.57% ($p< 0.001$).

The pooled results from these studies showed that serum DHT changed by a mean of +9.6% versus –90.2% at 24 months in the placebo and dutasteride groups respectively. Fifty-eight percent of dutasteride-treated patients achieved a 90% or greater reduction at 1 month and 85% of patients achieved 90% or greater reduction at 12 months. Serum testosterone changed by +5.4% versus +24.5% in the placebo and dutasteride groups at 24 months respectively. The TPV decreased significantly in dutasteride-treated patients starting at 1 month and continuing throughout the 24 months of the study ($p<0.001$). Clinical significant differences between the placebo and dutasteride-treated patients were also observed for AUA-SI scores. The changes from baseline were demonstrated as early as 3 months but reached significance at 6 months. Continued improvement was noted at 12, 18, and 24 months compared with the placebo. The maximal flow rate increased by 0.6 ml/second in the placebo group and 12.2 ml/second in the dutasteride

Table 2. **Adverse events associated with dutasteride use (24 month study period)**[6,7]

Adverse Events	Placebo (N=2158)	Dutasteride (N=2167)	Comparison between groups (*p*-value)
Impotence	4.0%	7.3%	< 0.001
Decreased libido	2.1%	4.2%	< 0.001
Gynecomastia	0.7%	2.3%	< 0.001
Ejaculation disorder	0.8%	2.2%	< 0.001

group at 24 months. The change from baseline was significant, as was the difference between dutasteride and placebo at 1 month on all measured endpoints. At 24 months serum PSA levels increased 15.8% from baseline in the placebo group compared to a 52.4% decrease in the dutasteride group. The incidence of AUR was 4.2% in the placebo-treated group compared to 1.8% in dutasteride-treated patients. The relative risk of AUR with the drug compared to placebo was 0.43 and the risk reduction was 57% ($p<0.001$).

The results of these studies indicate that, compared to placebo, dutasteride exhibits clinically significant effects in terms of DHT reduction, reduction of prostate volume and symptoms, flow rate improvement, and reduction of the risk of AUR and surgery over a 24-month period. In addition, the drug was well tolerated with a side effect profile that compared favorably with existing 5α-reductase inhibitors[10] (Table1 summarizes these results).

Dosage and Administration

Dutasteride is available as a 0.5 mg gelatin capsule. The recommended dose is a single capsule taken orally once a day. It should be swallowed whole and may be taken with or without food. No dosage adjustment is necessary for subjects with renal impairment or for the elderly. The effect of hepatic impairment on the pharmacokinetics of dutasteride has not been studied. Because the drug is extensively metabolized in the liver, exposure could be higher in hepatically impaired patients.[7]

Adverse Effects

Dutasteride was well tolerated in clinical trials. Overall, 75% of placebo treated patients and 77% of dutasteride-treated patients experienced an adverse event in the course of the 24-month study. The most common adverse events were musculoskeletal pain, upper respiratory tract infections, and ear, nose, and throat infections, Adverse events related to the drug were seen in 14% and 19% of placebo-treated and dutasteride-treated patients respectively. The most common drug-related adverse events were impotence, decreased libido, ejaculation disorders, and gynecomastia. Over the two-year treatment period, 9% of patients in the placebo and drug treatment arms withdrew from the study due to adverse events. Similar to finasteride, dutasteride may inhibit the development of the external genitalia of the male fetus; therefore, pregnant women should not handle the drug as it can be absorbed through the skin. Dutasteride may interfere with prostate cancer screening because it decreases serum concentrations of prostate specific antigen (PSA) by about 50%. Table 2 summarizes the adverse events associated with the use of dutasteride.

Drug Interactions

In vitro drug metabolism studies reveal that dutasteride is metabolized by human cytochrome isoenzyme CYP3A4.[7] In human studies the drug was found to be extensively metabolized with only less than 20% of the drug being excreted unchanged in feces. To date no clinical drug interaction studies have been done to evaluate the effects of CYP3A4 inhibitors on the pharmacokinetics of dutasteride. However, based on the in vitro data, blood concentrations of dutasteride may increase in the presence of inhibitors of CYP3A4 such as ritonavir, ketoconazole, verapamil, diltiazem, cimetidine and ciprofloxacin.[7] Clinical drug interaction studies have shown no pharmacokinetic or pharmacodynamic interactions between dutasteride and tamsulosin, terazosin, warfarin, digoxin and cholestyramine.

Cost

Based on three local community pharmacies, the mean retail price for a 30-day supply of dutasteride was $87.96. The price ranged from $84.74 to $97.19.

Summary

Dutasteride is the second 5α-reductase inhibitor approved by the FDA for the treatment of symptoms associated with BPH. The drug is a potent, competitive, and irreversible inhibitor of the two isoenzymes that convert testosterone to DHT. Dutasteride 0.5mg/day has been found to be safe and effective, reducing circulating DHT levels by 85% at week 1 and by 90% after 2 weeks of initiating treatment. Dutasteride represents an additional therapeutic option in the treatment of BPH; however, further studies are needed to determine if the drug offers any clinically significant advantages over finasteride.

References

1. Jonler M, Riehmann M, Bruskewitz R. Benign Prostatic Hyperplasia: Current Pharmacological Treatment. Drugs. 1994 Jan; 47(1): 66-81.
2. Isselbacher KJ, Braunwald E et al. Harrison's Principles of Internal Medicine. 13th edition, 1994. McGraw-Hill Inc. pp 1862-65.
3. Dull P, Reagan R, Bahnson R. Managing Benign Prostatic Hyperplasia. American Family Physician. 2002; 66(1): 77-83.
4. Bartsch G, Rittmaster RS, Klocker H. Dihydrotestosterone and the concept of 5alpha-reductase in human benign prostatic hyperplasia. World J Urology. 2002 Apr; 19(6): 413-25.
5. Vermeulen A, Giagulli VA et al. Hormonal effects of an orally active 4-azasteroid inhibitor of 5a-reductase in humans. Prostate 1989; 14:45-53.
6. Roehrborn CG, Boyle P et al. Efficacy and safety of a dual inhibitor of 5-alpha-reductase types1 and 2 (Dutasteride) in men with benign prostatic hyperplasia. Urology. 2002 Sep; 60(3): 434:41. Dutasteride Package Insert, 2001.
7. Gislosko PO et al. Clinical pharmacokinetics and pharmacodynamics of Dutasteride. British J Clinical Pharmacology. 1999; 47:53.
8. Bramson HN, Hermann D et al. Unique preclinical characteristics of CG745, a potent inhibitor of 5AR. J Pharm Exp Ther 1997; 282:1496-502.
9. McConnell JD, Bruskewitz R et al. Effect of finasteride on the risk of acute urinary retention and need for surgical treatment among men with benign prostatic hyperplasia. NEJM. 1998; 338:557-63.

Alinia® (nitazoxanide) is a new antiprotozoal agent used for the treatment of diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia* in pediatric patients 1 through 11 years of age. The usual dosage for children 12 to 47 months old is 5mL q12h for 3 days and for children 4 to 11 years old 10mL q12h for 3 days. This medication should be taken with food .

Relpax® (eletriptan hydrobromide) is a new 5-$HT_{1B,1D}$ receptor antagonist for the acute treatment of migraine attacks with or without aura. The usual dosage for adults is 20mg or 40mg at onset of headache. If it recurs after initial relief, may repeat after 2 hours. The maximum daily dose is 80mg. Avoid use in patients with severe hepatic impairment.

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