



# LA HEALTH-SYSTEM PHARMACIST

## Newsletter of the Louisiana Society of Health-System Pharmacists

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[www.lshp.org](http://www.lshp.org)

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### FROM THE DESK OF THE PRESIDENT

I am honored and excited to be President of the Louisiana Society of Health-System Pharmacists for 2009-2010. It is a privilege to serve a Society with a long history of great achievements encompassed by dedicated and motivated members. It is with much enthusiasm that I begin this year looking forward to visiting and working with each chapter, statewide, to prosper even more as an organization. I'm also very excited about working with my fellow officers and Board of Directors who serve LSHP bringing a wealth of knowledge, experience, and immeasurable devotion to assist me in achieving a successful term of office on your behalf.

I anticipate and look forward to a very productive year for our organization. Many of our members have already expressed a desire to participate on several of our committees and in their individual local chapters. The respective committee chair will contact each volunteer shortly after our summer retreat adjourns. If you have not volunteered, and would like to actively get involved with a committee of your choice, please contact me immediately. I am very confident that the committee chairs that I have chosen will lead each committee to successfully achieving the committee's goals. The chairs are each experienced members and they are each motivated in welcoming new members and having a successful year. I intend to serve as an ex-officio member on these committees in the capacity of assisting communication links between the committee members. As it has been done in the past, we will have board liaisons appointed to serve on these committees from the Board of Directors. This should ensure that the Board receives and acts in an informed manner on any and all recommendations placed forward by our committees.

The annual LSHP Retreat and Board of Directors Meeting is scheduled for August 8<sup>th</sup> and 9<sup>th</sup>. We will meet at the Methodist Conference Center in Woodworth, Louisiana. Typically, the retreat begins with lunch on Saturday at the conference center and ends early afternoon on Sunday. All officers, Board of Directors, and State Chapter Officers will be in attendance in addition to our Faculty LSHP advisors, student LSHP leaders, and select industry representatives that have been supporters of our programs. We will address both tabled and new agenda items, as well as have open discussions

on innovative approaches to growing our membership, assisting in the development of our regional chapters, and offering programs that bring pharmacists, pharmacy technicians, and pharmacy students into our professional society.

The 2009 LSHP Midyear Meeting is scheduled for October 10<sup>th</sup> at Sam's Town in Shreveport. Please mark your calendars today, and continue to watch our website for upcoming specifics pertaining to the Midyear meeting. The 2009 ASHP Midyear Clinical Meeting is scheduled for December 5-10 in Las Vegas. Registration for the ASHP Midyear opened on July 15<sup>th</sup>. Please make your travel and housing plans early.

In closing, as we begin a new year together, please keep in mind that each individual member's active participation will be needed to maintain the organizations current status. I challenge each member to encourage and invite other pharmacists, pharmacy technicians, and pharmacy students to become a member of LSHP and to become involved. Each member's insight is equally important, and as many of you have already contacted me with new ideas and suggestions, I encourage all members to freely contact me with suggestions or concerns. Our goal is to make LSHP a more productive, stronger, and larger organization, recognizing that we all must work together to achieve this goal.

Until we meet again at the LSHP Midyear meeting, I wish you all well, and that each of you remain safe, healthy, and excited about your membership in LSHP for the upcoming and future years.

Keturah Robinson  
LSHP President



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The LSHP  
Mid Year Meeting  
October 10, 2009  
Sam's Town Shreveport

Program topics tentatively  
scheduled include :

- Prevention and Treatment of Cancer -associated Thrombosis
- Prevention and Management of Febrile Neutropenia in Oncology Patients
- Pharmacotherapy of Alzheimer's Disease
- Treatment of Resistant Hypertension
- C.diff: Update on the incidence and known risk factors & what's new in treatment

**Reserve your hotel room today!  
LSHP's weekend room rate is \$125.  
Call Sam's Town at 877-429-0711 and  
be sure to mention the code,  
S10LSP9, to get the LSHP rate.  
This rate expires on September 7.**

**Don't forget to join us Friday night,  
October 9, for the Welcome Reception  
and fun at the Red River Revel!**

**Watch the LSHP Website,  
www.lshp.org, and your mailbox for  
more information!**

**LSHP Bimonthly Newsletter****LA HEALTH-SYSTEM PHARMACIST****Publisher Information**

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Please send article submissions to the newsletter editor, Dana Jamero, via email at [djamero@xula.edu](mailto:djamero@xula.edu).

## LSHP ULM Student Chapter Update

Monica Morgan  
President

Hello to all fellow LSHP members!

I hope everyone has been enjoying their summer thus far! I thoroughly enjoyed meeting all those who attended the LSHP annual meeting in New Orleans! With the beginning of a new school year quickly approaching, I would like to introduce the new ULM LSHP Student Chapter Executive Committee, beginning with our president-elect, Julie Sheridan. Victoria Williams was elected as our vice president and Breanne Peyton will be filling the position of secretary. Lastly, Denise Ghaedi, our treasurer, will be keeping our monetary business in order. I am very much looking forward to the upcoming year, as we have an extremely motivated and creative executive board who are as excited about our future profession as I am! As we finish our summer rotations, we will be planning meetings and events for the fall semester.

The following are a few goals that I have in mind for our ULM LSHP Student Chapter for the next year.

First, I would like to increase our active membership and provide the members with opportunities to participate in community service projects, such as brown bag events and emergency preparedness educational sessions. Secondly, I would like to increase the knowledge of LSHP members as to the various roles that hospital pharmacists play in the pharmaceutical field by hosting guest speakers with different institutional backgrounds. Lastly, I would like to increase participation at the mid-year and annual LSHP meetings by informing our members of the importance of attending and the benefits that they will receive from such activities.

Lastly, I sadly say goodbye to former president, Kristian Fruge, and would like to acknowledge him for all of the help he has given me and for his many prestigious awards and achievements! I hope to see many of you in the near future and am looking forward to leading an outstanding group of students! I hope everyone enjoys the remainder of the summer!



Comprehensive Pharmacy Services



### **DIRECTOR OF PHARMACY** **Lafayette General Medical Center, Lafayette, LA**

- Comprehensive Pharmacy Services, in partnership with Lafayette General Medical Center, is seeking an experienced hospital Director of Pharmacy to oversee the inpatient pharmacy's operations and to supervise a large staff. This is an exciting opportunity to expand clinical services and pharmacy automation.
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- A 301-bed acute-care hospital serving the Acadiana area, LGMC is currently undertaking a \$70 million renovation project to improve its existing buildings.

**Apply online directly at [www.cpspharm.com](http://www.cpspharm.com) or email/call/fax resume to Marie Rausch at [marie.rausch@cpspharm.com](mailto:marie.rausch@cpspharm.com), phone 763-354-1246, fax 763-354-1175.**

## South Central Chapter Update

Scott Dantonio, RPh  
SCLSHP Chapter President

First we would like to congratulate our chapter members on their recognition at the LSHP Annual Meeting in New Orleans. Tommy Mannino was elected to the LSHP Treasurer position. He was also named the Tommy Himel award winner for outstanding service to the organization. Lori Caruso was named the Outstanding Pharmacy Technician for the

year and Scott Dantonio was named the Outstanding Affiliate Chapter President. Our last chapter meeting was in April, with a talk given on IVIG. It was held at Sullivan's restaurant with an attendance of 25 people. Our next meeting will be July 22 and will consist of a live CE program presented by Mark Ryan of the Louisiana Poison Control Center. His talk will be on snakebites.

## Antibiotic, Antifungal, and Antiviral Dosage in Hepatic Impairment

Isabella T. Green, Pharm.D & Camtu Ho, Pharm.D.

Every day as we decide on a dosage for a medication for our patients many factors are taken into consideration. These factors include age, gender, weight, disease state, renal function and hepatic function. For example, a dosage calculated for a normal adult patient may not be sufficient for a pediatric patient and in turn may be too excessive for a geriatric patient. The same principle can be applied to patients experiencing hepatic impairment. For drugs that are metabolized hepatically, assessments must be made to determine whether or not a dosage adjustment is needed for that particular medication. The first values usually obtained in hepatically impaired patients are aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase concentrations. If these values are high, it indicates acute hepatic cellular damage. Although these values are widely known and used they are not the best determinant of hepatic drug metabolism. Better indicators of hepatic impairment are high serum bilirubin, low serum albumin, and prolonged prothrombin time. Bilirubin is important because it is metabolized by the liver and that can correlate to high drug accumulation. Both clotting factors and albumin are produced by the liver, therefore any change in production highlights a change in liver function. Changes that can lead to these abnormal values are impaired function of hepatocytes, impaired biliary elimination due to obstruction, ascites, and decreased first pass metabolism. Another measurement of hepatic dysfunction is the Child Pugh score (Table 1). For drugs with 60% or more of the compound metabolized in the liver, a score in excess of 10 suggests poor liver function, cirrhosis being the most severe, and a dosage reduction of 50%. A score of 8 to 9 suggests a moderate dose decrease of 25%. There are numerous drugs affected by hepatic dysfunction but in this discussion the focus will be on antibiotics, antifungals, and antivirals.

Several antibiotics, antifungals, and antivirals are affected by hepatic dysfunction. Antibiotics that should be avoided in severe liver disease are chloramphenicol, clindamycin, erythromycin, metronidazole, and rifampin. There is also significant accumulation of antibiotics such as cefotaxime, nafcillin, piperacillin, and sulfamethazole in both renal and hepatic dysfunction. If these drugs cannot be avoided in patient treatment than dosage adjustments must be recommended and liver function tests should be monitored. In a case report, a 42 year old female was placed on rifampin therapy for treatment of pruritis. The patient's baseline liver function tests before rifampin use were abnormally elevated. Upon the administration of rifampin 600 mg at night, the patient was relieved of the itching within ten days. After 4 weeks of

continuous rifampin therapy, the patient developed nausea, jaundice, and an increased prothrombin time to 18 seconds from 15 seconds. This case is an example of the dangers associated with treating hepatically impaired patients with medications that are extensively metabolized by the liver. The patient's rifampin therapy was discontinued and after six weeks the patient's lab values returned to normal.

In patients with concomitant diseases such as HIV and fungal infections, it is important for patients to use antiviral therapy as well as antifungal. In recent decades, the numbers of invasive fungal infections have increased and are very dangerous for patients who are immune compromised and those who have other conditions such as hepatic impairment. Antifungals that must be monitored in hepatic impairment include itraconazole, voriconazole, caspofungin, griseofulvin, and micafungin. For most of the medications listed, dosage adjustment is thought to be needed but currently there is no standardized reduction for these medications. Most research only discusses the symptoms that are found with liver toxicity and it is left up to the clinician to determine whether the benefits of antifungal therapy outweigh the risk. Moreover, antiviral treatment has even less information available than antibiotics and antifungals.

Antivirals are vital in the treatment armamentarium of HIV/AIDS. The development of antiviral medications are often placed on a fast track approval process so the drugs can reach their treatment population quickly. Due to the speedy development and approval of antivirals, there is less information about its impact on the hepatically impaired. Antivirals that are known to have some effect on the liver are abacavir, efavirenz, indinavir, lopinavir, ritonavir, nelfinavir, nevirapine, and zidovudine. In a case report, there was a definite correlation found between antivirals and liver toxicity. The patient was a newly diagnosed HIV patient that was placed on HAART and nevirapine therapy a month before admittance to the hospital. The patient developed symptoms including fever, malaise, nausea, diarrhea, and elevated liver enzymes. Upon discontinuation of therapy, the patient recovered within two weeks. Although this patient did not have hepatic impairment prior to antiviral therapy, the case is still relevant to the discussion in that if these drugs caused liver toxicity in a patient with normal liver function, perhaps a patient with pre-existing hepatic impairment would suffer the same outcome, if not worse. In a patient with hepatic impairment, there seems to be no doubt that some dosage adjustment is needed for both antivirals and antifungals but not enough research has been done

*Continued on following page.*

to determine what the need is for each specific drug.

In conclusion, antibiotics, antifungals, and antivirals are widely used in medicine today. Without these drugs, morbidity and mortality would most likely increase significantly. However, they still have their own risks. The dosages of these drugs must be substantial enough to allow effective treatment and yet low enough to avoid toxicity. In patients with hepatic impairment, it

is even more difficult to dose medications and not cause further harm to the liver. For most of the drugs mentioned above, dosage adjustment is needed but not enough research has been done to determine what adjustments need to be made. Table 2 gives the current recommendations for dosage adjustment in hepatic impairment for antibiotics, antifungals, and antivirals.

**Table 1**

Child-Pugh Score (points)	1	2	3
Billirubin (mg/dl)	1-2	2-3	>3
Albumin	>3.5	2.8-3.5	<2.8
Prothrombin Time (prolonged in seconds)	1-4	4-6	>6
Ascites	None	Mild	Moderate
Encephalopathy (graded)	None	1 and 2	3 and 4
Class A < 7 Class B = 7-9 Class C = 10-15 Reference: 1			

**Table 2**

Antibiotics, Antifungals, and Antivirals Recommendations in Hepatic Impairment	
<b>Antibiotics</b>	
Amoxicillin/Clauvanic acid	Monitor Liver enzymes in mild to moderate disease, contraindicated in severe disease
Azithromycin	Use caution, no specific guidelines
Cefotaxime	Moderate dose reduction needed in severe impairment
Ceftriaxone	Reduce dose when the patient has both renal and hepatic impairment
Chloramphenicol	Avoid use in severe hepatic impairment, increased toxicity may occur
Clindamycin	Adjustment recommended in severe hepatic impairment
Doxycycline	Avoid or use with caution
Erythromycin	May cause idiosyncratic hepatotoxicity
Indinavir	In mild or moderate impairment adjust dose to 600mg every 8 hours
Isoniazid	Reduce dose in severe impairment
Linezolid	No adjustment in mild or moderate, use caution in severe, not adequately studied
Metronidazole	Reduce dose in severe impairment
Moxifloxacin	Use not recommended in severe impairment
Nitrofurantoin	Cholestatic jaundice and chronic active hepatitis reported
Ofloxacin	Severe hepatic impairment, max dose is 400mg daily
Pyrazinamide	Reduce dose in hepatic impairment
Quinupristin/Dalfopristin	Dosage adjustment may be necessary
Rifampin (rifampicin)	Dosage reduction necessary
Sulfadiazine	Avoid in severe hepatic impairment
Sulfamethazole/trimethoprim	Manufacturer advises avoidance in severe impairment
Ticarcillin/Clauvanate potassium	2g of Ticarcillin every 24 hours when the patient has both renal and hepatic impairment ( Creatinine clearance < 10)
Tigecycline	In severe impairment, Child- Pugh Class C, use an intial dosage of 100mg followed by 25 mg every 12hrs

Table continued on following page.

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<b>Antifungals</b>	
Caspofungin	Mild dysfunction, no adjustment needed/ moderate dysfunction, Child Pugh 7-9, 35mg per day and use a loading dose of 70mg in invasive infection
Griseofulvin	Avoid in severe liver disease
Itraconazole	Adjustment may be needed, risk to benefit must be assessed
Micafungin	Use caution in mild to moderate impairment/ severe impairment not studied
Voriconazole	Mild to moderate impairment, Child-Pugh class A and B, use standard loading dose followed by 50% of the maintenance dose/ use in severe toxicity only if benefits out weight the risks.
<b>Antivirals</b>	
Abacavir	In mild dysfunction, Child-Pugh of 5-6, 200 mg twice daily, no information in severe impairment
Atazanavir sulfate	Atazanavir should be used with caution in patients with <u>mild-to-moderate hepatic impairment</u> . For patients with <u>moderate hepatic impairment (Child-Pugh Class B)</u> who have not experienced prior virologic failure, a dose reduction to 300 mg once daily should be considered. Atazanavir should not be used in patients with <u>severe hepatic impairment (Child-Pugh Class C)</u> . Atazanavir /ritonavir has not been studied in subjects with hepatic impairment and is not recommended. [
Efavirenz	Limited information, use with caution
Darunavir	Not recommended for use in patients with severe hepatic impairment
Fosamprenavir	<u>Mild Hepatic Impairment (Child-Pugh score ranging from 5 to 6):</u> Fosamprenavir should be used with caution at a reduced dosage of 700 mg twice daily without ritonavir (therapy-naïve) or 700 mg twice daily plus ritonavir 100 mg once daily (therapy-naïve or protease inhibitor-experienced). <u>Moderate Hepatic Impairment (Child-Pugh score ranging from 7 to 9):</u> Fosamprenavir should be used with caution at a reduced dosage of 700 mg twice daily without ritonavir (therapy-naïve), or 450 mg twice daily plus ritonavir 100 mg once daily (therapy-naïve or protease inhibitor-experienced). <u>Severe Hepatic Impairment (Child-Pugh score ranging from 10 to 15):</u> Fosamprenavir should be used with caution at a reduced dosage of 350 mg twice daily without ritonavir (therapy-naïve) or 300 mg twice daily plus ritonavir 100 mg once daily (therapy-naïve or protease inhibitor-experienced).
Lopinavir + Ritonavir	Plasma level increases in mild to moderate impairment, AUC of lopinavir may increase 30%
Nelfinavir	Use caution, insufficient data
Nevirapine	Not recommended with moderate to severe impairment
Ritonavir	Monitor in moderate impairment, use caution in severe impairment
Saquinavir	Contraindicated in hepatic impairment
Zidovudine	Drug accumulation may occur, use 100mg every 8 hours or 50% of the normal dose
Note : Drugs not mentioned may still need to be monitored when used in hepatic impairment	

**References**

- Dipiro, Joseph T. et al. Pharmacotherapy: a Pathophysiological Approach, 7th edition. New York: McGraw-Hill, 2008.
- Gokengin, deniz. et al. Hepatic Adverse Events during Highly Active Antiretroviral Therapy containing Nevirapine: A Case Report. Annals of Clinical Microbiology and Antimicrobials. 16 September 2002.
- Hilts, Alexandra E. et al. Antiretroviral Dosing in Patients with Organ Dysfunction. AIDS. 1998.
- Lacy, Charles F. et al. Drug Information Handbook, Fourteenth edition. Hudson, Ohio: Lexi-Comp.2006. Pages
- Prince, M. I. et al. Hepatitis and Liver Dysfunction with Rifampicin Therapy for Pruritis in Primary Biliary Cirrhosis. Gut.2002
- Wong-Beringer, Annie. et al. Systemic Anti Fungal Therapy: New Options, New Challenges. Pharmacotherapy Publications.2003
- Mehta, Dinesh K. et al. WHO Model Formulary, World Health Organization. 2004. Pages 722-726.
- Lexiva® Package insert 2009.
- Reyataz® Package insert 2008.
- PREZISTA® (darunavir) Package insert 2008.

## Febuxostat (Uloric®): A New Ally in the Chronic Treatment of Hyperuricemia in Gout

LeShay Wesson, Pharm.D. and Shannon Bagnet-Finley, Pharm.D.

Over the last four decades, the prevalence of gout has increased to the staggering amount of nearly 5 million people in the United States. The rapid rise of this debilitating disease has prompted the development of a new urate-lowering agent known as febuxostat (Uloric®). Indicated for the chronic management of hyperuricemia in patients with gout, febuxostat, marketed by Takeda Pharmaceuticals, was approved by the FDA in 2009.

Gout is a condition that develops as a result of accumulated urate crystals in the joints or surrounding tissues, leading to vast inflammation and pain. Hyperuricemia serves as a precursor to gout and occurs when there are increased levels of uric acid in the blood ( $>6.8$  mg/dL) for extended periods of time. The presence of long term hyperuricemia leads to the formation of monosodium urate crystals causing severe, acute episodes of pain, redness, swelling, and tenderness around the joints. Patient's who experience several, reoccurring intense attacks, are at an increased risk of developing urate crystal deposits, known as tophi. These crystals form under the patient's skin and are ultimately responsible for their increased risk of deformities and morbidity associated with gout. NSAIDs, colchicine, or corticosteroids are often used to treat the symptoms associated with the acute flares, while urate lowering therapies, including xanthine oxidase inhibitors and uricosuric agents, have been utilized in the chronic management. An increase in gout flares has been observed during the initiation of therapy with febuxostat or allopurinol; therefore it is recommended that prophylactic dosing of NSAIDs or colchicine be started concurrently for up to 6 months of therapy. If the gouty flare occurs while taking febuxostat or allopurinol, it is not necessary to discontinue them. The starting dose for febuxostat is 40 mg by mouth once daily. If the patient's serum uric acid levels are not at a therapeutic goal of  $\leq 6$  mg/dL 2 weeks after starting therapy, the dosage should be increased to 80 mg per day. Reaching this therapeutic goal will help prevent future flares and painful symptoms.

Febuxostat belongs to a class of urate-lowering agents known as the xanthine oxidase (XO) inhibitors. Xanthine oxidase inhibitors exert their mechanism by decreasing the synthesis of uric acid, thus reducing serum levels. Xanthine oxidase inhibitors prevent the conversion of hypoxanthine to uric acid in purine metabolism. Uric acid has no physiological role in the body and is predominantly excreted by the kidneys. In gout patients with hyperuricemia, uric acid accumulates as a result of overproduction and/or underexcretion. Overproduction may occur due to a diet that is high in purine contents (i.e. liver, seafood, alcoholic beverages, etc.) or an abnormality in the metabolic enzymes, 5-phosphoribyl-1-pyrophosphate (PRPP) and hypoxanthine guanine phosphoribyl transferase (HGPRT). Both of these enzymes function in purine biosynthesis. Underexcretion may be due to some degree of renal insufficiency or other disease-related

complications.

Prior to the addition of febuxostat to the market, gout patients with hyperuricemia were predominantly treated with allopurinol, a purine analogue xanthine oxidase inhibitor. Allopurinol served as the chief medication used to treat gout in those patients who were diagnosed as being "overproducers" for the last four decades. It has proven to be safe and efficacious; however, disadvantages such as the increased possibility of patients experiencing a life-threatening hypersensitivity reaction and the need for renal dose adjustments based on creatinine clearance sparked the interest of the development of this new agent. It is thought that the renal-adjusted dose schedules of allopurinol has caused many patients to receive suboptimal therapy and consequently are unable to achieve their therapeutic reduced serum uric acid level of  $< 6$  mg/dL.

Febuxostat poses an alternative to treating uric acid overproducing-gout patients. It is metabolized hepatically and does not require dosage adjustments for renal or hepatic insufficient patients. It can be taken without regard to meals or antacids. It is contraindicated with theophylline, mercaptopurine, or azathioprine due to the risk of increasing these agents' plasma concentrations. In a comparative study conducted by Schumacher et al, the efficacy of febuxostat was compared to that of allopurinol in a 28-week randomized, double-blind, parallel-group trial. In this study, 1,072 participants with hyperuricemia ( $\geq 8.0$  mg/dL) and gout were randomized to treatment groups to be given once-daily dosing of febuxostat 80, 120, and 240 mg, allopurinol 100 mg if SCr  $>1.5$  to  $\leq 2.0$  mg/dL or 300 mg if SCr was  $\leq 1.5$  mg/dL, or placebo for a period of 28 weeks. After randomization, 1,062 participants were assessed for reduced serum uric acid levels. Most of the subjects were between the ages of 45-65 years old (56%), male (94%), and white (78%). The primary endpoint was reaching and maintaining a serum urate levels below 6.0 mg/dL for a period of 3 months. The results showed that both febuxostat and allopurinol significantly achieved the primary endpoint versus the placebo ( $p < 0.001$ ). Of the treatment groups, 48% of the febuxostat 80 mg group (126/262), 65% of the febuxostat 120 mg group (175/269), and 69% of the febuxostat 240 mg group (92/134) versus 22% of the combined allopurinol 100 mg and 300 mg (20/268) treatment groups reached the primary endpoint. None of the placebo treatment group (0/134) reached the primary endpoint. Overall, a notably larger amount of patients in the febuxostat treatment groups maintained the reduced serum urate level of 6 mg/dL compared to the allopurinol and placebo group. In patients with baseline serum urate levels of  $\geq 10$  mg/dL, 36% of participants receiving 80 mg febuxostat, 52% of patients receiving 120 mg febuxostat, and 66% of patients receiving 240 mg febuxostat maintained their goal serum urate level for 3 month. In contrast, only 10% of the allopurinol combined group and 0% of the placebo group reached this end point. In

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this trial, febuxostat was also shown to be efficacious in mild to moderately impaired renal function. These patients were defined as having a CrCl of 30-89 ml/min. Of subjects receiving 80 mg, 120 mg, and 240 mg of febuxostat, 44%, 46%, and 60% attained the three month goal of reduced uric acid levels. Adverse events were comparable in all of the treatment groups, with the most common ones being abnormal liver function tests, upper respiratory tract infections, rash, and diarrhea.

In comparison to allopurinol, the data suggest that febuxostat (Uloric®) is an efficacious alternative for the chronic management of hyperuricemia in patients with gout. Because this agent dose not require renal dose adjustments, patients in this population may reach and maintain serum uric levels of <6 mg/dL making this agent an ideal alternative for patients with mild to moderate renal insufficiency. Like allopurinol, febuxostat is also associated with an increase in transaminase levels and non fatal thromboembolic events. It is recommended that close monitoring of patients at risk of elevated liver enzymes, MI or stroke be closely monitored during either therapy. Further clinical significance concerning the increased abnormal liver enzymes, increased risk of nonfatal MI or stroke, and proper, efficient renal dosing of allopurinol should be investigated. Adequately retaining serum urate levels below 6 mg/dL will prevent acute gout flares, and in the long-term improve the patient's quality of life, therefore febuxostat shows great promise in the treatment of hyperuricemia in gout patients who have failed to respond to allopurinol or who may have renal insufficiency.

## References

- Edwards, NL. (2008). "Treatment-failure gout: a moving target". *Arthritis & Rheumatism*. 58(9):2587-2590.
- Eggebeen, AT. (2007). "Gout: An Update". *American Family Physician*. 76(6): 801-808.
- "Gout". (2007). *Mayo Clinic*. Retrieved Feb. 2, 2009 from <http://www.mayoclinic.com/gout>.
- Hair, FL. (2008). "Febuxostat". *Drugs*. 68(13): 1865-1874.
- Harris, MD, LB Siegel, and JA Alloway. (1999). "Gout and hyperuricemia". *American Family Physician*. 59(4): 925-934.
- Product information for Uloric. (2009). Takeda Pharmaceuticals America, Inc. Deersfield, IL 60015. Retrieved March 22, 2009 from <http://www.ulooric.com>.
- Schumacher, HR. et al. (2008). "Effects of febuxostat versus allopurinol in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial". *Arthritis Care and Research*. 59(11): 1540-1548.
- Qazi, Y and JW Lohr. (2007). "Hyperuricemia". *Emedicine from WebMD*. Retrieved Feb. 2, 2009 from <http://www.emedicine.medscape.com/hyperuricemia>.
- Yu, KH. (2007). "Febuxostat: a novel non-purine selective inhibitor of xanthine oxidase for the treatment of hyperuricemia in gout". *Recent Patents on Inflammation and Allergy Drug Discovery*. 1: 69-75.