



DIVISION OF MEDICAL ASSISTANCE PROGRAMS

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Authority

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July 25<sup>th</sup>, 2013

**Division Statement on High Cost and/or Marginally Beneficial Drugs**

This statement was delivered as the DMAP UPDATE at the P&T Committee Meeting on July 25th, 2013, by Pharmacy Service Program manager, Trevor Douglass.

We, DMAP, applaud the work done by this committee on the important subject of HCMB drugs and appreciate the collaboration between you and the HERC.

We believe the HCMB issue is important. Apparently, so do you and a lot of other folks---the industry, advocates for various diseases, OHP clients and CCOs.

We realize, as do you, in the course of your continued work to establish a Preferred Drug List, often you will identify drugs that, as a committee believe should be flagged as HCMB; we want to work with you to do so.

However, the question is going to be what becomes of a HCMB drug list and how will it be used. After DMAP assessed the P&T committee's and the public input from the prior committee meetings it has become clear there are problems with using a HCMB drug list as you and the HERC originally intended. PhRMA raised concerns that federal drug rebate statutes require ALL rebateable drugs to have a path by which the state Medicaid program provides reimbursement when medically appropriate.

Federal law does allow DMAP to place controls on the use of all drugs to ensure they are being prescribed for FDA approved indications or supported by compendia. But when DMAP does place controls on drugs... DMAP must provide a clear process by which the drugs are paid for when indicated for use in treatment of a diagnosis that falls on a funded line of the prioritized list. Therefore, the plan to use the prioritized list to not pay for a drug that has been placed on a HCMB list is not something DMAP will pursue.

DMAP would like to ask the P & T committee to continue to identify drugs you feel rise to the level of HCMB. A rebateable drug will be provided a pathway for coverage... which is what you currently do when you recommend PA criteria you believe is appropriate in order for a prescriber to seek reimbursement for the drug. The committee may additionally consider functional assessments and case management when considering the ongoing/continued use of drugs found on the HCMB list. Development of a HCMB list of drugs can help inform the department, partners, clinicians and other participants in the health care delivery system of the costs and benefit of these drugs. Again, it is important to understand that drugs found on this list will be provided a clear path for coverage and will NOT be excluded from coverage. Furthermore, it is important to note that the development of any PA criteria continue to occur in a transparent manner and that a clear process be established and conducted for each drug being placed on the HCMB table. The process, whether you do the work or seek a help from a subcommittee is your choice we and the staff will work with you.

Thanks again for your work you have done of this issue and bringing it to our attention. We wish we could have proceeded as you original proposed but are unable to do to federal law as pointed out by PhRMA's counsel. However your continued work around these drugs will help DMAP provide better health outcomes at lower costs.

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## Multiple Sclerosis Center



July 22, 2013

Dear Sir or Madam:

It has come to our attention that your Pharmacy & Therapeutics Committee will soon be reviewing coverage for Ampyra (Dalfampridine). As providers for approximately 3000 Multiple Sclerosis patients in the State of Oregon, we would like to share with you its role in our MS patient care.

One of the most important concepts regarding Ampyra is that it does *not* belong in the category of "MS Disease modifying Therapy" for the purposes of formulary review, because it is not an immunomodulator or immune suppressing agent. Rather, it works to improve the *symptoms* of MS, specifically the speed of ambulation. Although its exact mechanism of action is unknown, Ampyra is thought to increase nerve conduction by preventing potassium leakage along demyelinated axons, thereby increasing nerve conduction. Whereas the traditional DMTs seek to prevent neuronal damage by modifying or suppressing autoimmunity, Ampyra seeks to improve the electrical efficiency of the nerves which have already been damaged by MS. It is the only therapeutic agent of its class.

The prevalence of walking difficulty in the MS population is high, and in fact patients list it as the most feared complication of the disease (Heesen C, et al. *Mult Scler.* 2008;14:988-991). Patients in the Phase III trial who met criteria for treatment responders also had a positive impact on their MSWS score (a measure of ambulation's impact on Activities of Daily Living). There are several studies documenting that a 20 percent improvement in T25FW translates into meaningful improvements in ADLs (Holbari, J, et al. *Neurology*, 2013 Mar 27; Kaufman, M. et al. *Mult Scler.* 2000 Aug; 6(4) 286-90).

Examples of positive feedback we have had from our patients include improved walking endurance while shopping, getting the mail, reduced risk of falling, and ability to walk longer distances without having to rest. There is one patient in our clinic who had been benefitting from the drug as he walked long distances with clients as part of his job; we were terribly disappointed to hear that he had a severe fall within a week of being forced to come off the drug due to formulary issues with his insurance company.

We certainly realize that the medication has high cost, does not work for every patient, and carries a small risk of seizure. Even knowing this, we feel it is critical to have Ampyra available for patients for whom improvement in ambulation would make a significant positive impact on quality of life and safety (e.g. allow them to continue working, or better maintain their independence). To prevent indiscriminant use of the drug, we agree it is reasonable to have patients re-assessed after being on therapy, to determine whether the improvement in ambulation was meaningfully impacting their ADLs, with plans to discontinue therapy for non-responders.

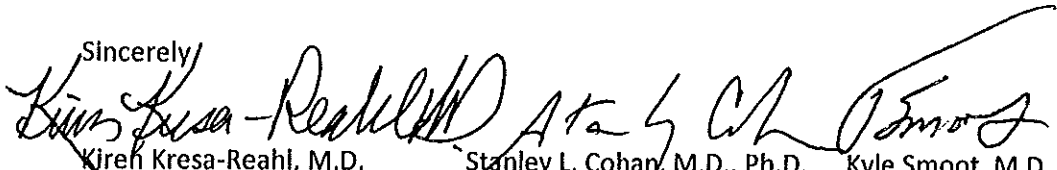
We respectfully request that you re-evaluate your current approval criteria. Specifically criteria #7, requiring patients to "have a walking disability requiring the use of a walking aide", and the requirement

Kiren J. Kresa-Reahl, MD  
Kyle E. Smoot, MD  
Leah Gaedeke, MSN, FNP-BC

for "25 foot walk time be between 8 and 45 seconds"). The phase III clinical trial for FDA approval did not require patients to utilize a walking device to enter the trial, and the most recent Ampyra trial measuring 6 minute walk times did not restrict patients with timed walks under 8 seconds, but rather included patients who had any gait disturbance due to MS. The imposition of these restrictions would leave many patients who might benefit significantly from the benefits of Ampyra without access to the medication.

Many thanks for your attention to our remarks. Please feel free to call any of us if you have any further questions.

Sincerely,



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**National  
Multiple Sclerosis  
Society**  
Oregon Chapter

Oregon Pharmacy and Therapeutics Committee  
Drug Use Research and Management Program  
OHA Division of Medical Assistance Programs  
500 Summer Street NE, E35  
Salem, OR 97301-1079

July 25, 2013

Dear Members of the Pharmacy and Therapeutics Committee:

Thank you for the opportunity to provide comments today on the benefits of Ampyra for people living with multiple sclerosis. On behalf of the 7,700 people living with multiple sclerosis in Oregon, I offer the following testimony for your consideration.

Multiple Sclerosis (MS) is an unpredictable, often disabling disease of the central nervous system. MS interrupts the flow of information within the brain, and between the brain and body. MS can cause blurred vision, loss of balance, poor coordination, slurred speech, tremors, numbness, extreme fatigue, cognitive deficits, and even paralysis and blindness. The progress, severity and specific symptoms of MS in any one person cannot yet be predicted, but advances in research and treatment are moving us closer to a world free of MS. Because symptoms vary so much in people living with MS, as well as response to treatments, the National MS Society believes that all treatments available to treat the disease and its' diverse symptoms should be available to all those who live with this disease. Treatment decisions are best determined jointly by the treating physician and the patient.

Difficulty with walking, balance issues and coordination problems are among the most common symptoms of MS. In fact, in a 2008 online survey conducted on behalf of Acorda Therapeutics, Inc. and the National MS Society, 41% of people living with MS in the survey reported having difficulty walking. 70% of those with difficulty walking cited it was the most challenging aspect of having MS. Only 34% of people with MS with difficulty walking were employed.<sup>1</sup> Ampyra, which received FDA approval in January 2010 "to improve walking ability in patients with MS", is the only FDA approved agent with this indication. Ampyra works only for a relatively small percent of people living with MS, but it can be life changing for those who see the benefits.

In examining the benefits of Ampyra, I urge you to consider broader impact than simply the increase in walking speed. First, consider what one gains from an increase in walking speed. Bladder and bowel dysfunction are other common symptoms experienced by those living with MS. An increase in walking speed can greatly help someone manage these sometimes isolating symptoms.

Among those taking Ampyra who improved in walking speed, there was also a statistically significant improvement in leg strength.<sup>2</sup> This improvement in leg strength could mean an exercise program is now a viable option for the individual.

Based on data from the online survey previously mentioned, people with MS who have difficulty walking generally report not only negative impact on their mobility, but also restricted activities, a negative impact on emotional health and a higher need for assistance in performing daily tasks. Please consider this statement from the article cited about the online study: "The findings reported here showed that difficulty walking has a broad and substantial impact on daily activities, social function, employment and socioeconomic status." The benefits an individual living with MS may find from Ampyra are not just in walking speed, but in all of these things- improved social function, positive impact on daily activities and improved opportunities for employment and socioeconomic status.

I would like to share with you the story of EJ Levy, diagnosed with MS in her early thirties. EJ was an active hiker and skier with a fast-paced internet job. Within two years EJ had left her job and could walk very short distances with a cane, using a wheelchair for longer distances. Today, thanks to Ampyra, EJ is able to walk without a cane and hikes up to five miles. She says, "It's about quality of life. Having my mobility and my life back is priceless."

Diagnosed with MS in February 2012, Chet Arnett said Ampyra has made a difference. "My balance is better with Ampyra, as is my walking." He's seen overall improvements in steadiness, walking, and coordination, and that offers hope to continue living independently. He explained "A year ago I was worried about falling and needed assistance from others. I have much more confidence now and feel secure in my movement." Chet goes to the store, gets his mail, exercises and completes other daily activities without worry. "If I couldn't take Ampyra, my MS symptoms would be more pronounced, I wouldn't be able to walk as well as I do, and I'd need more help."

In your consideration of Ampyra, please think about EJ and Chet and the broad benefits people with MS have due to increased mobility. These benefits are more than marginal. For the percent of people for whom Ampyra works, the changes they see are substantial.

Thank you for your time and consideration. Please let me know if there is any additional information the National MS Society may provide.

Sincerely,



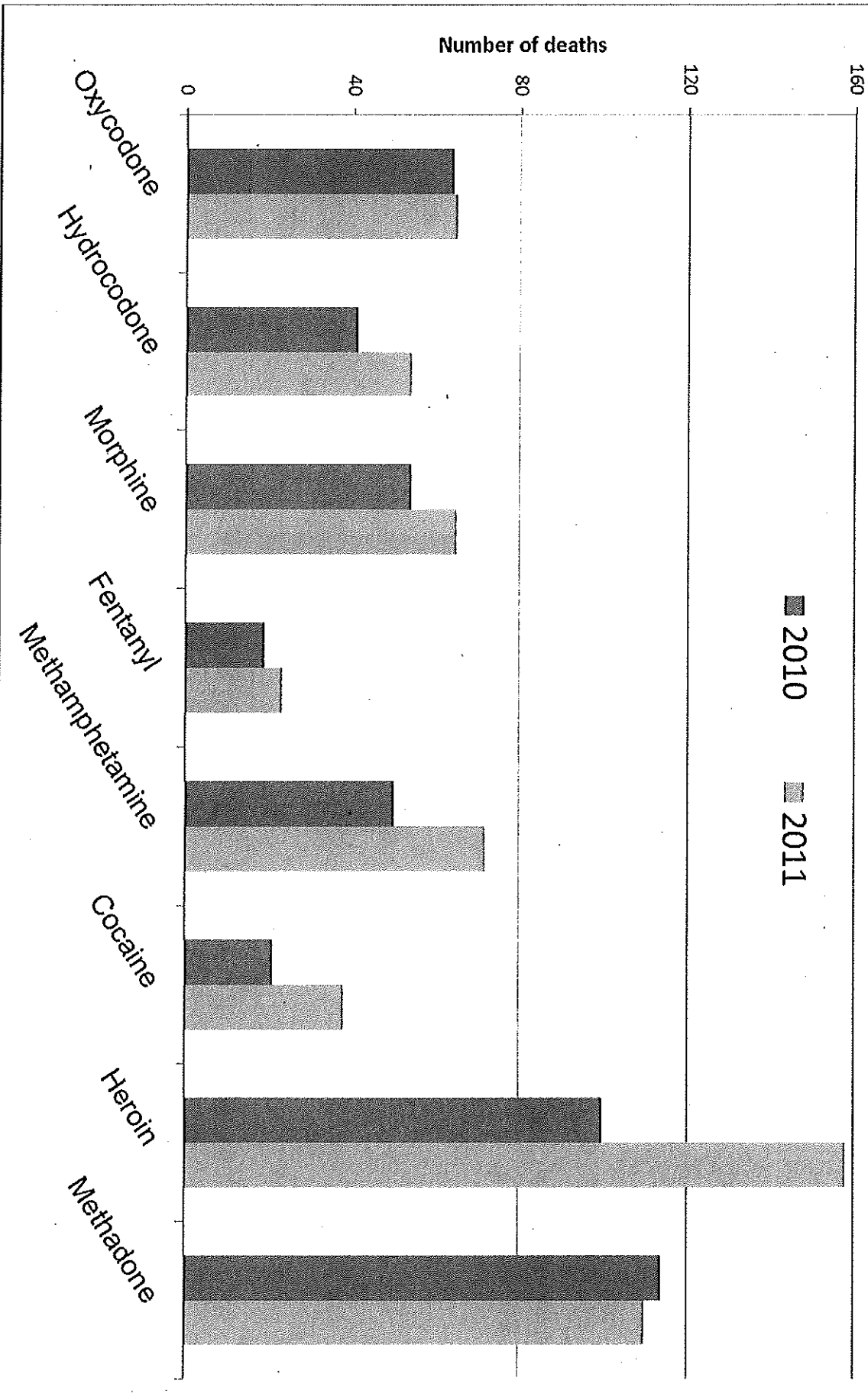
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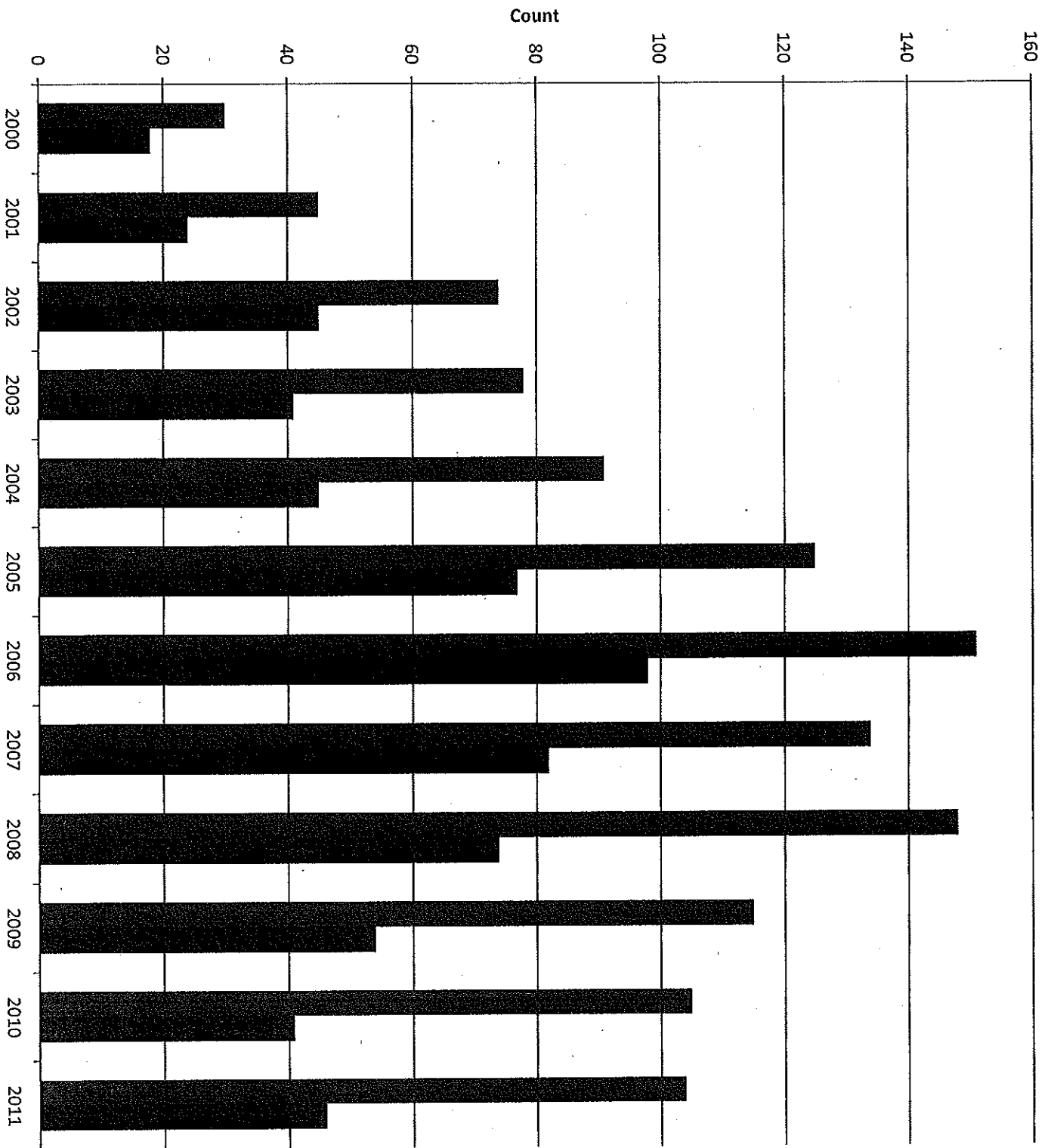
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<sup>1</sup>LaRocca, Nicholas G.; *Impact of Walking Impairment in Multiple Sclerosis*. Patient 2011; 4(3): 189-201.

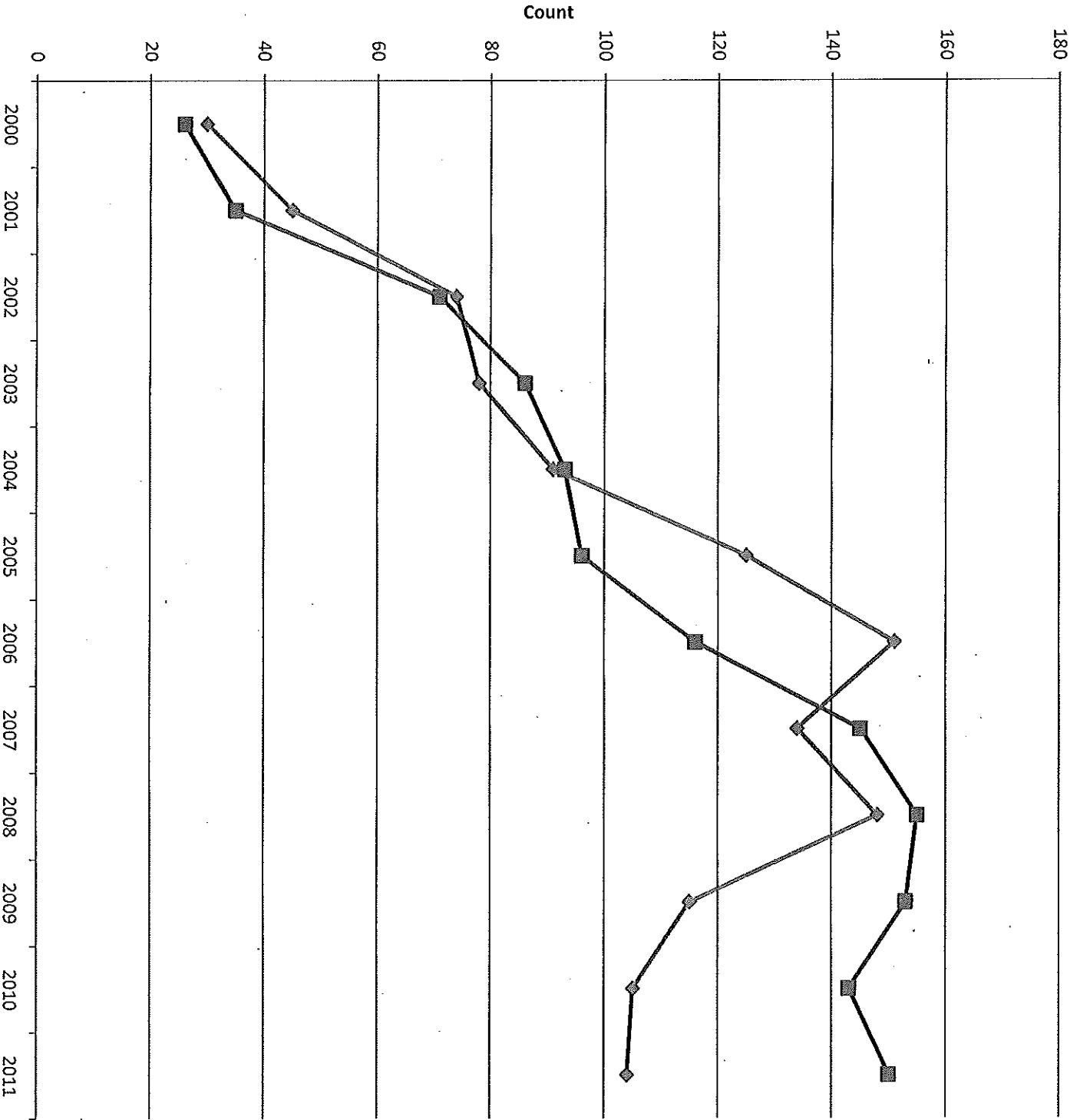
<sup>2</sup>Goodman AD, Brown TR, Cohen JA, Krupp LB, Schapiro R, Schwid SR, Cohen R, Marinucci LN, Blight AR; Fampridine MS-F202 Study Group. *Dose comparison trial of sustained-release fampridine in multiple sclerosis*, Neurology. 2008 Oct 7;71(15):1134-41. Epub 2008 Jul 30.

# Keyword search of literal text for drugs Oregon 2010-2011 (Preliminary)





■ Methadone related death  
 ■ Methadone only for death



◆ Methadone deaths  
 ■ Methadone hospitalizations



## Comments to ADHD Therapeutic Class Scan (OSU Drug Use Research & Management Program / Oregon Health Authority)

### Background

**Month/Year of Review:** July 2013

**PDL Class:** ADHD

**Source Document:** Drug Effectiveness Review Project

**Current Status of PDL Class:**

- Preferred Agents: AMPHETAMINE ASPARTATE/AMPHETAMINE/D-AMPHETAMINE, DEXMETHYLPHENIDATE, DEXTROAMPHETAMINE, FOCALIN® (BRAND ONLY), LISDEXAMFETAMINE, METHYLPHENIDATE
- Non-Preferred Agents: ATOMOXETINE, GUANFACINE, CLONIDINE

**Previous Recommendation:**

Due to a lack of comparative efficacy or effectiveness data, do not consider extended release formulations of clonidine and guanfacine as clinically superior to other stimulant and non-stimulant ADHD treatments.

**Current PA criteria:**

Prior authorization is required for non-preferred drugs to ensure coverage only for OHP covered diagnoses and restrict to doses supported by the medical literature. This PA does not concern drugs in STC 07 or 11; however, these drugs are not to be encouraged. The State is prohibited from prior authorizing Class 11 drugs by statute. These include:

- Armodafinil (Nuvigil®)
- Atomoxetine (Strattera®)
- Modafanil (Provigil®)

**Methods:**

A Medline OVID search was conducted. The search was limited to English language articles of controlled trials conducted between 2011 to second week in May 2013. A total of 245 citations resulted from the initial MEDLINE search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After a review of titles and abstracts for inclusion, seven relevant head-to-head clinical trials were identified and discussed. From these, two specifically discussed atomoxetine.

1. Weisler et al.<sup>1</sup> conducted a study comparing bavisant with traditional ADHD medications for symptom control over 42 weeks. This good quality, randomized, double-blind, placebo-controlled, multi-center trial evaluated 3 dosages of bavisant with atomoxetine, methylphenidate and placebo; 430 adult patients were randomized. The primary outcome was mean change from baseline in the total ADHD-RS-IV score at day 42. None of the bavisant groups showed a significance difference from placebo; statistical analysis was performed only for the 10 mg strength (mean difference: -8.8 vs. -12.2,  $p = 0.161$ ). Mean change from baseline in the total ADHD-RS-IV score at day 42 was superior to placebo in the atomoxetine (-15.3) and methylphenidate (-15.7) groups (both,  $p < 0.005$ ).
2. Yildiz et al.<sup>2</sup> conducted an open-label study to compare the efficacy and safety of atomoxetine and methylphenidate for ADHD. Children ( $n=25$ ) aged 8 to 14 years old were randomized to 12 weeks of treatment with either medication. According to the primary efficacy parameter of improvement in

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<sup>1</sup> Weisler RH, Pandina GJ, Daly EJ, Cooper K, Gassmann-Mayer C. Randomized Clinical Study of a Histamine H3 Receptor Antagonist for the Treatment of Adults with Attention-Deficit Hyperactivity Disorder. *CNS Drugs*. 2012;26(5):421–434. doi:10.2165/11631990-000000000-00000.

<sup>2</sup> Yildiz O, Sismanlar SG, Memik NC, Karakaya I, Agaoglu B. Atomoxetine and Methylphenidate Treatment in Children with ADHD: The Efficacy, Tolerability and Effects on Executive Functions. *Child Psychiatry & Human Development*. 2010;42(3):257–269. doi:10.1007/s10578-010-0212-3.

scores of the Clinical Global Impression Scales Severity and Improvement (CGI-S, CGI), treatment responses were not significantly different between the two groups. There was also no difference found on a parent rated behavior assessment tool ( T-DSM-IV) or in discontinuations due to adverse effects. According to the review, this was a poor quality study with many opportunities for bias.

In addition, the Cochrane Collection, Dynamed and Medline OVID were searched for high quality systematic reviews. Three new systematic reviews were identified. From these, two specifically discussed atomoxetine.

1. Van Wyk et al.<sup>3</sup> assessed how Oppositional Defiant Disorder (ODD), inattention, and hyperactivity-impulsivity affect the response to atomoxetine versus methylphenidate. Seven randomized control trials (n=1,391) conducted on children and adolescents with ADHD aged 6 to 16 years old were included in the systematic review. The primary outcome was a  $\geq 40\%$  reduction in the ADHD Rating Scale-IV (ADHD-RS-IV). The mean difference (atomoxetine minus methylphenidate) in response rates for patients with ODD was 0.6% (95% CI = -11.9% to 13.1%). Response rate differences for patients meeting the threshold for inattention or hyperactivity-impulsivity were -3.1% (95% CI = -11.5% to 5.3%) and -4.9% (95% CI = -14.3% to 4.4%), respectively. Comorbid ODD did not alter symptom response to either product.
2. Hanwella et al.<sup>4</sup> performed a systematic review with head to head randomized clinical trials comparing the efficacy of atomoxetine versus methylphenidate for ADHD symptom improvement in children with ADHD aged 6 to 16 years (n=2762). The outcome studied was a comparison in change in ADHD-RS-IV score. The standardized mean difference (SMD) was used as a measure of effect size. Analysis did not find a significant difference in efficacy between methylphenidate and atomoxetine (SMD = 0.09, 95% CI -0.08 to 0.26). Synthesis of data from eight trials found no significant difference in response rates (RR = 0.93, 95% CI 0.76 to 1.14, p=0.49).

## Comments

We thank the OSU Drug Use Research & Management Program and the Oregon Health Authority for the opportunity to provide comments to the information provided in this ADHD Scan. We would respectfully ask for consideration of atomoxetine to be moved to the ADHD preferred agent list so that ADHD patients can equally benefit from a non-stimulant medication that has been shown to provide comparable effectiveness as methylphenidate in these systematic reviews and head to head clinical trials.

This included two head to head clinical trials (Weisler et al. 2012 and Yilidiz et al. 2010) and two systematic reviews (Van Wyk et al. 2011 and Hanwella et al. 2011), noted in your evaluation, which specifically discussed atomoxetine. The findings included no statistically significant differences between atomoxetine and methylphenidate.

Jenny Blackham, MPH  
Outcomes Liaison  
Eli Lilly and Company

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<sup>3</sup> Van Wyk GW, Hazell PL, Kohn MR, Granger RE, Walton RJ. How Oppositionality, Inattention, and Hyperactivity Affect Response to Atomoxetine Versus Methylphenidate: A Pooled Meta-Analysis. *Journal of Attention Disorders*. 2011;16(4):314–324. doi:10.1177/1087054710389989.

<sup>4</sup> Hanwella R, Senanayake M, de Silva V. Comparative efficacy and acceptability of methylphenidate and atomoxetine in treatment of attention deficit hyperactivity disorder in children and adolescents: a meta-analysis. *BMC Psychiatry*. 2011;11(1):176. doi:10.1186/1471-244X-11-176.

## Oregon Medicaid Drug Class Review: Controller Medications for Asthma Studies for *Flovent*

This response may include reference to information about *Flovent*<sup>®</sup> *Diskus*<sup>®</sup> (fluticasone propionate inhalation powder), *Flovent HFA*<sup>®</sup> (fluticasone propionate) Inhalation Aerosol, *Advair Diskus*<sup>®</sup> (fluticasone propionate and salmeterol inhalation powder) and *Advair HFA*<sup>®</sup> (fluticasone propionate and salmeterol) Inhalation Aerosol

- As part of the public comment process, the following abstracts and citations for *Flovent* listed below have been identified for possible inclusion. The citations/abstracts were identified by searching Embase for the time period of March 2010 to the present date. The search terms included; clinical trial, efficacy, safety, safe, fluticasone propionate, asthma. The studies were included based on the principles of evidence-based medicine and, therefore, references may not be all-inclusive.
- *Advair HFA* is not indicated for use in children less than 12 years of age.
- Important safety information is found in the attached Prescribing Information.
- The prescribing information for this product contains a boxed warning. Please consult the WARNING section of the attached prescribing information for further details and for important safety information.

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**Efficacy and tolerability of salmeterol/fluticasone propionate versus fluticasone propionate in asthma patients: a randomized, double-blind study.**

**Lee YS, Lin HC, Huang CD, Lee KY, Liu CY, Yu CT, Wang CH, Kuo HP.  
Chang Gung Med J. 2011 Jul-Aug;34(4):382-94.**

Abstract BACKGROUND: A combination of salmeterol and fluticasone propionate (SAL/FP) has been shown to be effective in the treatment of asthma. We compared the efficacy and tolerability of SAL/FP (50/250 µg) with fluticasone propionate (FP) 250 µg administered twice daily for 2 weeks in treating patients with mild to moderate asthma. METHODS: This was a randomized, double-blind study in adult patients with symptomatic asthma that was not controlled by 1000 µg/d inhaled corticosteroids (ICS) alone. 48 asthmatics were randomized to receive 2 inhalations of SAL/FP 50/250 µg bis in die (BID) or 2 inhalations of FP 250 µg BID, both delivered via Accuhaler device, for 2 weeks. The primary objective

was the mean change from baseline in the mean morning peak expiratory flow (PEF) over the two week period. Other parameters included lung function, daily asthma symptom scores, evening PEF, percentage of days free of rescue medication use and daily rescue medication use. Tolerability was assessed by adverse events spontaneously elicited at clinic visits. **RESULTS:** 46 patients provided evaluable efficacy for analysis. The morning PEF improved significantly throughout the two weeks of treatment compared with baseline in the SAL/FP group. Mean morning PEF was 23.0 L/min higher in SAL/FP group than in FP group ( $p = 0.013$ ). The change of forced expiratory volume in one second (FEV1) from baseline was greater in SAL/FP group compared to FP group ( $p = 0.048$ ). There were similar effects on day-time and night-time symptom scores, percentage symptom free days and nights and usage of salbutamol. 70.8% of the patients receiving SAL/FP were satisfied with the treatment, while only 26.1% of patients receiving FP alone were ( $p = 0.020$ ). No death or acute exacerbation occurred. **CONCLUSION:** SAL/FP 50/250  $\mu\text{g}$  was safe and effective, and had a high level of patient satisfaction resulting in significantly greater increases in morning PEF and FEV1 compared to the use of FP 250  $\mu\text{g}$  alone.

### **Evaluation impact of long-term usage of inhaled fluticasone propionate on ocular functions in children with asthma.**

**Emin O, Fatih M, Mustafa O, Nedim S, Osman C.**  
**Steroids. 2011 May;76(6):548-52**

**Abstract OBJECTIVE:** Although systemic, topical, and periocular corticosteroid administration have long been associated with ocular side effects, there has been little evidence to suggest that long-term inhaled corticosteroids can cause ocular side effects. The aim of this study was to evaluate the effects of long term treatment inhaled fluticasone propionate spray usage the recommended dose on some ocular functions in pediatric patients with asthma **METHODS:** The study group consisted of 266 prepubertal children with asthma who had used inhaled fluticasone propionate spray at 3-6 years intermittently. One hundred and sixty children who were newly diagnosed with asthma without any treatment made up the control group. Schirmer test results, central corneal thickness, visual acuity, intraocular pressure, cataract formation, keratometry and tear break-up time compared between study and control groups. **RESULTS:** The ages of the 266 study patients (150 male) were between 7 and 11 years. The average age ( $\pm\text{SEM}$ ) was  $8.2\pm 1.7$  years, and the mean ( $\pm\text{SEM}$ ) a daily dose of 323  $\mu\text{g}$  (range 250-450  $\mu\text{g}$ ) inhaled fluticasone propionate spray, with  $865.2\pm 215$  g total steroid use during treatment. Eye functions including cataract formation, corneal ectasia, ocular hypertension or glaucoma, and dry eye were not observed in any of the patients in the study group and were not correlated with total steroid dosage ( $t=0.150$ ,  $p=0.384$ ). **CONCLUSION:** Our findings suggest that long-term intermittent treatment for 3-6 years with inhaled fluticasone propionate spray, as much as average 320  $\mu\text{g}$  daily, in children with asthma seems to be safe for some eye functions Copyright © 2011 Elsevier Inc. All rights reserved.

### **Management of asthma in school age children on therapy (MASCOT): A randomised, double-blind, placebo controlled, parallel study of efficacy and safety**

**Lenney W., McKay A.J., Tudur Smith C., Williamson P.R., James M. and Price D.**  
**Health Technology Assessment 2013 17:4 (1-238)**

**Background:** Asthma affects one in eight children in the UK. National management guidelines have been available for many years but, unlike in adults, studies in children have been few, with their methodologies often based on inappropriate adult models. Sound medical evidence in support of the national guidelines for asthma management in children is lacking. The MASCOT study has been developed to address this need. **Objectives:** To determine whether adding salmeterol or montelukast to low-dose inhaled corticosteroids (ICSs) can reduce the number of exacerbations requiring treatment with oral corticosteroids in children with uncontrolled asthma. **Design:** A randomised, double-blind, placebo-

controlled trial with a 4-week run-in period on a fluticasone propionate inhaler (100 µg twice daily) with inhaler technique correction. Patients who met the post run-in period eligibility criteria were randomised in the ratio of 1: 1: 1 and were followed for 48 weeks. Setting: Secondary care hospitals based in England and Scotland with recruitment from primary and secondary care. Participants: Children aged 6-14 years with asthma requiring frequent short-acting beta-2 agonist relief, with symptoms of asthma resulting in nocturnal waking and/or asthma that has interfered with usual activities. Interventions: Three groups were compared: (1) inhaled fluticasone propionate 100 µg twice daily plus placebo tablet once daily; (2) inhaled fluticasone propionate 100 µg and salmeterol 50 µg twice daily (combination inhaler) plus placebo tablet once daily; and (3) inhaled fluticasone propionate 100 µg twice daily plus montelukast 5-mg tablet once daily. Main outcome measures: The primary outcome was the number of exacerbations requiring treatment with oral corticosteroids over 48 weeks. Secondary outcome measures included quality of life as measured by the Paediatric Asthma Quality of Life Questionnaire with Standardised Activities [PAQLQ(S)] and the Paediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ); time from randomisation to first exacerbation requiring treatment with a short course of oral corticosteroids; school attendance; hospital admissions; amount of rescue beta-2 agonist therapy prescribed; time from randomisation to treatment withdrawal (because of lack of efficacy or side effects); lung function at 48 weeks (as assessed by spirometry); cost-effectiveness; adverse events. Results: The study was closed prematurely because of poor recruitment and the target sample size of 450 was not achieved. In total, 898 children were screened to enter the trial, 166 were registered for the 4-week run-in period and 63 were randomised (group 1: 19, group 2: 23, group 3: 21), with 38 contributing data for the primary outcome analysis. There were no significant differences between groups for any of the outcomes. Adverse events were similar between the groups except for nervous system disorders, which were more frequently reported on fluticasone plus montelukast. Conclusions: Based on the results of the MASCOT study it is not possible to conclude whether adding salmeterol or montelukast to ICSs can reduce the number of exacerbations requiring treatment with oral corticosteroids in children with uncontrolled asthma. © Queen's Printer and Controller of HMSO 2013

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### **Effect of montelukast for treatment of asthma in cigarette smokers**

**Price D., Popov T.A., Bjermer L., Lu S., Petrovic R., Vandormael K., Mehta A., Strus J.D., Polos P.G. and Philip G.**

**Journal of Allergy and Clinical Immunology 2013 131:3 (763-771.e6)**

Objective: Many asthmatic patients are unable to quit cigarettes; therefore information is needed on treatment options for smokers. This study evaluates 10 mg/d montelukast and 250 µg of fluticasone propionate twice daily, each compared with placebo, in patients with self-reported active smoking (unable to quit) and asthma. Methods: Patients (ages 18-55 years, with asthma  $\geq 1$  year], FEV1 of 60% to 90% of predicted value, airway reversibility  $\geq 12\%$ ], and self-reported active smoking  $\geq 0.5$  to  $\leq 2$  packs per day]) were randomized (after a 3-week, single-blind, placebo, run-in period) to 1 of 3 parallel, 6-month, double-blind treatment arms. The primary efficacy end point was the percentage of days with asthma control during treatment. Adverse experiences (AEs) were also evaluated. Results: There were 347, 336, and 336 patients randomized to montelukast, fluticasone, and placebo, respectively. The mean percentage of days with asthma control over 6 months of treatment was 45% (montelukast,  $P < .05$  vs placebo), 49% (fluticasone,  $P < .001$  vs placebo), and 39% (placebo); the difference between montelukast and fluticasone was not significant ( $P = .14$ ). Patients with a smoking history of  $\leq 11$  pack years (the median value) tended to show more benefit with fluticasone, whereas those with a smoking history of  $>11$  pack years tended to show more benefit with montelukast. AEs occurred in similar proportions among

treatment groups. Conclusions: In a population of asthmatic patients actively smoking cigarettes, both 10 mg/d montelukast and 250 µg of fluticasone propionate twice daily significantly increased the mean percentage of days with asthma control compared with placebo. © 2013 American Academy of Allergy, Asthma & Immunology

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### **Health-related quality of life assessment using St. George's respiratory questionnaire in asthmatics on inhaled corticosteroids**

**Sabin T., Parthasarathi G. and Padukudru M.A.**  
**Lung India 2012 29:1 (35-43)**

Context: Chronic diseases like asthma have significant effects on patients' health-related quality of life (HRQoL). HRQoL measures additional indices as compared to objective measurements like spirometry. Aims: To assess and compare disease-specific quality of life in asthma patients using St. George's Respiratory Questionnaire (SGRQ) receiving fluticasone, beclomethasone, and budesonide (BUD). Settings and Design: A prospective, open label, randomized, parallel group study conducted at a tertiary care teaching hospital in South India. Materials and Methods: A 6-month follow-up of 277 patients with mild, moderate, and severe persistent asthma was randomized to receive fluticasone propionate (FP), BUD, or beclomethasone dipropionate (BDP) in equipotent doses according to their global initiative on asthma (GINA) severity. Statistical analysis used: Data analyzed using SPSS version: 13.0. General linear-repeated measures using the post-hoc bonferroni method assessed significance between treatment groups. Results: Significant decrease ( $P < 0.05$ ) in each SGRQ domains and total scores as well as improvement in FEV<sub>1</sub> ( $P < 0.05$ ) was observed in all study subjects. A significant early response ( $P < 0.05$ ) was noted after 15 days treatment in patients receiving FP with respect to SGRQ (activity, impact and total) scores and dyspnea indices, but not FEV<sub>1</sub>. This improvement with FP was due to its greater effect in patients with moderate and severe persistent asthma. No difference was noted subsequently in all outcome measures studied until 6 months. Conclusions: There was evidence for an early QoL improvement to FP as compared to BUD or BDP in moderate and severe persistent asthma. Subsequently, the three ICS showed similar improvements in lung functions and dyspnea indices throughout the study.

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### **Effectiveness of fluticasone propionate and rare adverse effects in preschoolers with asthma**

**Djukanović R., Wilson S.J., Moore W.C., Koenig S.M., Laviolette M., Bleecker E.R., Davis W.B., Doherty D.E., Olivenstein R., Israel E., Kavuru M.S., Kleerup E., Reilly D.S., Yancey S.W., Edwards L.D., Stauffer J.L., Dorinsky P.M. and Jarjour N.N.**  
**Respiratory Medicine 2010 104:10 (1425-1435)**

Background: Airway inflammation is a key pathological feature of asthma which underlies its clinical presentation. Objectives: To examine whether adding a leukotriene modifier to an inhaled corticosteroid produces further clinical and/or anti-inflammatory benefits in patients symptomatic on short-acting  $\beta_2$ -agonists. Methods: Patients uncontrolled on short-acting  $\beta_2$ -agonists were treated for 12 weeks with either fluticasone propionate (100 mcg BD) or fluticasone propionate (100 mcg BD) and montelukast (10 mg QD) in a randomized, double-blind, parallel group study. Bronchoscopy with endobronchial biopsy

and bronchoalveolar lavage (BAL) was performed before and after treatment to compare effects on airway inflammation. Results: Of 103 subjects enrolled, 89 subjects completed treatment and 82 subjects had matched pair biopsy samples. Submucosal eosinophil counts, the primary endpoint, and asthma control improved to similar extents after both treatments ( $p \leq 0.008$ ). Both treatments significantly reduced submucosal mast cell, CD3+, CD4+, CD8+ and CD25+ cell counts. Submucosal mast cell reduction was greater in the fluticasone propionate plus montelukast group. There were no differences between treatments in BAL markers of inflammation or thickness of sub-epithelial collagen. Conclusions: Low-dose fluticasone propionate significantly improves clinical disease control and reduces airway inflammation in asthma patients uncontrolled with short-acting  $\beta$ 2-agonists without further improvement when montelukast is added to low-dose fluticasone propionate. © 2010 Published by Elsevier Ltd

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### **Fluticasone propionate-salmeterol versus inhaled corticosteroids plus montelukast: Outcomes study in pediatric patients with asthma**

**Stanford R.H., Shah M. and D'Souza A.O.**

**Journal of Asthma and Allergy 2013 :6 (1-10)**

Background: The purpose of this study (GSK ADA111194) was to compare asthma-related health care utilization and costs associated with fluticasone propionate (an inhaled corticosteroid [ICS]) and salmeterol (a long-acting beta-agonist) in a single inhalation device (fluticasone propionate-salmeterol) versus the combination of ICS + montelukast in the treatment of pediatric patients with asthma. Methods: This was a retrospective, observational cohort study using a large health insurance claims database spanning January 1, 2000 to January 31, 2008. The target population was patients aged 4-11 years with at least one pharmacy claim for fluticasone propionate-salmeterol, any ICS, or montelukast during the study period. The date of first claim for the medication of interest was deemed the index date. Patients were required to be continuously eligible to receive health care services one year prior to and 30 days after the index date, and have at least one claim with an ICD-9-CM code for asthma (493.xx) in the one-year pre-index period. Patients with prescriptions for fluticasone propionate-salmeterol, ICS + montelukast, or long-acting beta-agonists during the pre-index period were excluded. Patients were matched on a 1:1 basis according to three variables, i.e., pre-index use of oral corticosteroids, ICS, and presence of pre-index respiratory related hospitalizations/emergency department visits. The risk of asthma-related hospitalization, combined hospitalization/emergency department visit, and monthly asthma-related costs were assessed using multivariate methods. Results: Of the 3001 patients identified, 2231 patients were on fluticasone propionate-salmeterol and 770 were on ICS + montelukast. After matching, there were 747 pairs of fluticasone propionate-salmeterol and ICS + montelukast patients, which were well matched for baseline characteristics. Patients who started fluticasone propionate-salmeterol compared with patients on ICS + montelukast had a significantly ( $P < 0.02$ ) lower rate of asthma-related hospitalizations (0.3% versus 3.5%) and asthma-related hospitalizations/emergency department visits (3.5% versus 5.7%). After controlling for baseline and patient characteristics, fluticasone propionate-salmeterol users were associated with a significantly lower risk of an asthma-related hospitalization (adjusted hazard ratio 0.039; 95% confidence interval 0.004-0.408) or hospitalization/ emergency department visit (hazard ratio 0.441; 95% confidence interval 0.225-0.864), and \$151 (95% confidence interval 67-346) lower asthma-related monthly costs compared with ICS + montelukast. Conclusion: In patients aged 4-11 years with asthma, use of fluticasone propionate-salmeterol was associated with lower asthma-related health care utilization and costs compared with use of ICS + montelukast. © 2013 Stanford et al, publisher and licensee Dove Medical Press Ltd.

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## **Bone mineral density and associated parameters in pre-pubertal children with asthma treated with long-term fluticasone propionate**

**Ozkaya E., Çakir E., Uzuner S., Erenberk U. and Dundaröz M.R.**  
**Allergologia et Immunopathologia 2013 41:2 (102-107)**

**Aims:** The primary aim of the objective of the study was to determine the effects of long-term treatment with the recommended dose of inhaled fluticasone propionate spray usage on bone mineral status in children with asthma. **Methods:** This cross-sectional, case-control study was of 270 pre-pubertal children with asthma, who had used inhaled fluticasone propionate at a mean daily dose of 200. µg (range: 200-350. µg) for at least 5 years. The bone mineral density (BMD) of the lumbar spine was measured by dual-energy X-ray absorptiometry (DEXA). The results were compared to untreated controls (n=200), who were newly diagnosed children with asthma without any corticosteroid treatment. **Results:** The 270 study patients (175 males) were aged between 6 and 13 years. The average age ( $\pm$ SEM) was 9.2 $\pm$ 0.6 years, and the mean ( $\pm$ SEM) steroid dosage used was 183.3 $\pm$ 57.0. µg daily, with 236.5 $\pm$ 17.2. g total steroid use during treatment. Between the study and the control groups, no significant difference was observed in BMD ( $p > 0.05$ ). **Conclusion:** The findings suggest that long-term periodical treatment for 5 years with inhaled fluticasone propionate, 100. µg twice daily, in children with asthma revealed no negative effect on bone mineral density by using DEXA. © 2011 SEICAP.

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## **Comparative effectiveness of extrafine hydrofluoroalkane beclometasone (EF HFA-BDP) and fluticasone propionate (FP) in smoking asthmatic patients-a retrospective, real-life observational study in a UK primary care asthma population**

**Price D., Martin R.J., Milton-Edwards M., Israel E., Roche N., Burden A., Von Ziegenweidt J., Gould S.E., Hillyer E. and Colice G.L.**  
**Journal of Allergy and Clinical Immunology 2013 131:2 SUPPL. 1 (AB3)**

**RATIONALE:** Smoking is a common reason for poor asthma control, and associated with corticosteroid resistance, yet smokers are usually excluded from asthma trials. This study investigates the effect of stepping up inhaled corticosteroid (ICS) dose for smokers, non-smokers and ex-smokers. **METHODS:** Retrospective study using the UK Clinical Practice and Optimum Patient Care Research Databases. Adult patients ( $\geq 30$  years) stepped-up their existing ICS ( $\geq 50\%$  increase in dose) as either EF HFA-BDP or FP. Patients were required to have  $\geq 2$  prescriptions for ICS during both the year prior to and following step-up, and/or a diagnostic code for asthma. Smoking status was defined by database codes, with ex-smokers first recorded as ex-smokers over age 30. EF HFA-BDP patients (step-up year post 2005) were matched 1:1 to FP patients on demographic, disease and smoking characteristics in the baseline year. Exacerbation rates (asthma-related inpatient admissions; emergency room attendances; or use of acute oral steroids) were calculated for outcome year and adjusted for baseline confounders. Modeling explored interactions between treatment effects and smoking status. **RESULTS:** Median (IQR) doses (mcg) at step-up were 400 (200, 400) for EF HFA-BDP and 500 (500,1000) for FP. Exacerbation rates were comparable for non-smokers with rate ratio (95% CI) 0.84 (0.68, 1.03) for EF HFA-BDP compared with FP; n5575 per treatment arm, but significantly lower for EF HFA-BDP for current and ex-smokers 0.64 (0.48, 0.85); n5314. **CONCLUSIONS:** Results suggest a differential treatment effect between ex-smokers/smokers and non-smokers. It is likely that the smaller particle formulation of EF HFA-BDP plays some role in this effect. Copyright 2013 Elsevier B.V., All rights reserved.

## **The effect of inhaled corticosteroids on hypothalamic-pituitary-adrenal axis**



**Moghaddam K.G., Rashidi N., Meybodi H.A., Rezaie N., Montazeri M., Heshmat R. and Annabestani Z.**  
**Indian Journal of Pharmacology 2012 44:3 (314-318)**

**Objectives:** The aim of this study was to compare systemic effects of high-dose fluticasone propionate (FP) and beclomethasone dipropionate (BDP) via pressurized metered dose inhaler on adrenal and pulmonary function tests. **Materials and Methods:** A total of 66 patients with newly diagnosed moderate persistent asthma without previous use of asthma medications participated in this single blind, randomized, parallel design study. FP or BDP increased to 1 500 µg/d in 62 patients who had not received oral or IV corticosteroids in the previous six months. Possible effects of BDP and FP on adrenal function were evaluated by free cortisol level at baseline and after Synacthen test (250 µg). Fasting plasma glucose and pulmonary function tests were also assessed. Similar tests were repeated 3 weeks after increasing dose of inhaled corticosteroids to 1 500 µg/d. **Results:** No statistically significant suppression was found in geometric means of cortisol level post treatment in both groups. After treatment in FP group, mean forced expiratory volume in one second (FEV1) and mean forced vital capacity (FVC) values improved by 0.17 l (5.66% ± 13.91, P=0.031) and 0.18 l (5.09% ± 10.29, P=0.010), respectively. Although FEV1 and FVC improved in BDP group but was not statistically significant. Oral candidiasis and hoarseness were observed in 6.5% patients receiving BDP, but hoarseness was found in 3.2% patients in FP group (P=0.288). **Conclusions:** The results indicate that safety profiles of high doses of BDP and FP with respect to adrenal function are similar, but FP is more efficacious than that of BDP in improving pulmonary function test.

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### **Effectiveness of fluticasone propionate and rare adverse effects in preschoolers with asthma**

**Bajraktarevic A., Maglajlija S., Penava S., Begovic B., Selimovic A., Dzinovic A., Guzin Z., Frankic T., Gutic J., Djulepa Djurdjevic A., Roncevic Z., Sporisevic L. and Prnjavorac Rakic B.**  
**Allergy: European Journal of Allergy and Clinical Immunology 2011 66 SUPPL. 94 (584)**

**Background:** Inflammation is recognized as an important component in the pathogenesis of asthma. Fluticasone propionate is a synthetic, trifluorinated glucocorticoid with potent anti-inflammatory activity. This medication must be used regularly to prevent the wheezing and shortness of breath caused by asthma or obstructive bronchitis, or some rare types of emphysema in children. **Aim:** To determine if the early use of inhaled fluticasone propionate in wheezy preschooler children older helps to prevent loss of lung function and progression of asthma later in school-childhood. **Method:** This study was a randomized, double-blind, placebo-controlled prospective trial using other therapy from golden rules and guidelines GINA modified for children. Spirometry and induced sputum for differential cell counts and albumin, 2-macroglobulin and blood eosinophil and, interleukins factor levels were obtained before treatment and two, six and twenty four hours after treatment in children with asthma in age between 2 to 7 years of ages during first decade of new millennium. **Result:** When glucocorticoids are discontinued, asthma stability may persist for several days or longer. The total clearance of fluticasone propionate is high, with renal clearance accounting for less than 0.02% of the total. This medication does not work immediately, because it is preventive and prolonged action. The most children (99.5%) older than two years in Bosnia and Herzegovina using this medication do not have serious side effects. Preschoolers with recurrent wheezing or asthma had less wheezing or asthma exacerbations and improve their symptoms and lung function during treatment with inhaled corticosteroids in the most cases (98%) in our ten years study. **Discussion:** The precise mechanisms of glucocorticoid action in asthma are unknown. The safety and effectiveness of Fluticasone propionate inhalation aerosol in children below two years of age have not

been established. Conclusion: Fluticasone propionate inhalation aerosol is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required. The authors concluded that inhaled fluticasone given twice daily over a 6-month period improved asthmatic symptoms and had no significant adverse effects on growth.

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### **Safety and efficacy of long-term treatment with fluticasone propionate and salmeterol via DISKUS versus fluticasone propionate alone**

**Kerwin E., Prazma C.M., Sutton L. and Stempel D.A.**  
**Clinical Research and Regulatory Affairs 2011 28:1 (14-21)**

This 52 week study (ADA109057; ClinicalTrials.gov identifier: NCT00452348) was designed to assess the safety and efficacy of fluticasone propionate (FP)/salmeterol 250/50 mcg via DISKUS (FSC) vs FP 250 mcg in subjects with persistent asthma symptomatic on FP 100 mcg. The objective was to demonstrate superiority in lung function (FEV1) of FSC 250/50 mcg vs FP 250 mcg. Secondary objectives included AM PEF, percentage of symptom-free days, and rate of asthma attacks. Three hundred and ten subjects received FSC 250/50 mcg and 318 subjects received FP 250 mcg, both administered twice daily following a 14-21 days of open-label FP 100 mcg. Treatment with FSC 250/50 mcg resulted in an improvement in lung function vs FP 250 mcg ( $p = 0.09$ ). Additionally, treatment with FSC 250/50 mcg improved AM PEF and increased the percentage of symptom-free days. The asthma attack rate was similar between treatments, as was the safety profile. FSC 250/50 mcg demonstrated improvements in lung function and asthma control vs FP 250 mcg, although statistically significant differences were not consistent. The differences may be representative of this population with less severe disease at entry. In patients with mild-to-moderate persistent asthma FSC offers improved parameters of asthma control compared with ICS alone. © 2011 Informa Healthcare USA, Inc

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### **Therapeutical effect of montelukast and/or fluticasone monotherapy upon children with bronchial asthma**

**Markova N.**  
**Allergy: European Journal of Allergy and Clinical Immunology 2010 65 SUPPL. 92 (540)**

Phenotype differences of BA-allergic and non-allergic cases along with the degree of severity suggest various effectiveness and choice of controlling medicine. Altogether, these factors require precise anamnesis and continuous monitoring. Objective: The purpose of this research is to compare the effects of the two main groups of medicines (LT and IC) for the treatment of Asthma. Material and methods: Subject to the research are 356 children of ages between 2 and 10 years divided in two main etiological groups: Virus-induced asthma (259) and Atopic pollen asthma (97). In terms of severity, there are cases of intermittent, mild, and moderate severe persisting asthma during a 3-year period of monitoring. 288

children were treated with montelukast in daily doses of 4 or 5 mg according to their age, and 68 children were treated with fluticasone propionate in doses of 200 µg divided into two intakes. The therapy is seasonal: for Pollen asthma from April to September, and for Virus induced asthma from October to March. The clinical effect shall be reported as complete, partial no effect. We monitored the medicine's effect upon coughing and rhinitis symptoms. Monitoring of PEF was performed for children over 4 years. Monitoring of Eo was performed for all patients. Results: Complete control of symptoms of Virus-induced asthma was reported for 61% of the cases treated with montelukast and for 79% of those treated with fluticasone. Coughing was completely affected in 46% of those treated with montelukast and in 75% of those treated with fluticasone. In the Atopic pollen asthma, better results were reported for treatment with montelukast: 86% and 75% for complete control of the two indicators respectively. The high results above 70% are present in the treatment with fluticasone as well. When Pollen rhinitis is present in the patients treated with fluticasone, additional treatment with Antihistamines or local nasal remedy is necessary. Completely affected rhinitis symptoms were observed in 73% of the children treated with montelukast. The Eo evidently decreased in patients treated. Improvement in PEF of more than 20% was reported for patients treated with fluticasone. Conclusion: Montelukast appears to be a suitable choice for treatment of intermittent and mild persisting asthma. For cases of mild persisting Asthma unaffected by the treatment with montelukast, the choice of fluticasone remains more appropriate.

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### **A comparison of clinical efficacy and safety of ciclesonide with fluticasone in 1:1 and 1:2 dose ratios in the treatment of bronchial asthma (systematic review and meta-analysis)**

**Kokot M., Wojciechowski P., Stozek A., Rogóz A., Rys P., Plisko R. and Władysiuk M.  
American Journal of Respiratory and Critical Care Medicine 2011 183:1 Meeting Abstracts**

**Introduction/Rationale:** The main aim of the asthma therapy is to control the disease by preventing exacerbations, maintaining proper lung function and reducing the need of rescue therapies. This goal should be achieved with no or minimal drug side effects. The most effective drugs used in asthma controlling are inhaled corticosteroids. Ciclesonide and fluticasone are two of four inhaled corticosteroids currently available in Europe. The purpose of this study was to compare clinical efficacy and safety of ciclesonide (CIC) with fluticasone (FP) in the treatment of bronchial asthma. **Methods:** Comparison of efficacy and safety of analyzed drugs was based on randomized controlled trials (RCTs) identified by means of systematic review, carried out according to the Cochrane Collaboration guidelines. The most important medical databases (EMBASE, MEDLINE and CENTRAL) were searched. Two reviewers independently selected trials, assessed their quality and extracted data. Critical appraisal of included studies was performed using the Jadad scale. Meta-analysis of head-to-head trials was performed to compare safety and efficacy of CIC with FP. **Results:** The search in medical databases resulted in total number of 1278 identified publications (including repeated titles). 155 positions were qualified for full text analysis. Finally 10 trials met predefined inclusion criteria and were suitable for further analysis. All studies had apparel design. Methodological credibility of the trials included in the analysis was good or medium in most cases. Efficacy of CIC was comparable to FP in both, 1:1 and 1:2 dose ratios with respect to reduction in risk of asthma exacerbations, improvement in proportion of symptoms-free days, rescue medication-free days and improvement in asthma symptoms. The quality of life was significantly improved in CIC group as compared to FP in 1:1 dose ratio (WMD = 0.12 [0.04, 0.019]). Moreover, no significant differences between treatment options in either dose range were observed as regards improvement in spirometric parameters. Analysis of safety measures revealed that treatment with CIC, as compared to FP in 1:1 daily dose range, was associated with statistically significant risk reduction of adverse events possibly related to study medication (RR = 0.57 [0.39, 0.83]; NNT = 16.89 [10.24, 48.18]) and candidosis (RR = 0.31 [0.17, 0.56], NNT = 32.74 [22.23, 61.99]). No significant difference was

found as regard withdrawal from study due to adverse event and lack of efficacy. Conclusion: The study suggests CIC vs FP has a favorable efficacy/safety ratio.

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**A randomized, open labeled, comparative study to assess the efficacy and safety of controller medications as add on to inhaled corticosteroid and long-acting  $\beta$ 2 agonist in the treatment of moderate-to-severe persistent asthma**

**Patel Y.A., Patel P., Bavadia H., Dave J. and Tripathi C.B.  
Journal of Postgraduate Medicine 2010 56:4 (270-274)**

Background : The goal of asthma therapy is to achieve clinical control and near normal lung functions. Many patients with persistent asthma fail to achieve this goal with a single controller medication add on to a inhaled corticosteroid. We have checked whether another controller medication add on to inhaled corticosteroid and long-acting 2 agonist helps in achieving the asthma goal or not. Objectives : To identify the effect of controller medication add on to inhaled corticosteroid and the long-acting 2 agonist on the clinical symptom, lung function, and compliance in patients with asthma. Materials and Methods : We conducted a randomized, open-labeled, comparative trial in 50 participants with moderate-to-severe persistent asthma. The study duration was of 10 weeks. During the first two weeks of the run-in period all the participants received a dry powder inhaler drug delivery of budesonide (400 mcg/day) and formoterol (12 mcg/day) combination. At the end of the run-in period the participants were randomly allocated into three groups: group A (n = 16) received oral montelukast (10 mg/day); group B (n = 17) received oral doxophylline (400 mg/day), and group C (n = 17) received inhaled budesonide (400 mcg) as add on to the above-mentioned drugs of the run-in period. The primary outcome was improvement in forced expiratory volume at 1 second (FEV 1 ). Results : All the participants of the three groups had significant improvement in FEV 1 (P < 0.001) and asthma symptoms at the end of 10 weeks. The mean increase in FEV 1 (% of predicted) from the baseline, in groups A, B, and C was: 24.6; 21.33, and 19.86%, respectively. Conclusions : All add on controller medications helped, with a significant improvement of lung functions and asthma symptoms.

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**Comparison of asthma-related outcomes and costs in pediatric subjects that received low dose fluticasone propionate or montelukast in a large managed care population**

**Stanford R.H., Shah M. and Chaudhari S.  
Annals of Allergy, Asthma and Immunology 2010 105:5 (A46-A47)**

Objective: To compare asthma-related exacerbations (emergency department (ED) or inpatient (IP) visit) and related cost in pediatric patients aged 4-11 years that received either fluticasone propionate 44 mcg (FP44) or montelukast (MON). Methods: Retrospective observational study utilizing a large managed care database with linked pharmacy and medical claims. Patients with  $\geq 1$  pharmacy claim FP44 or MON between January 1, 2000 through June 30, 2008 (4-11 years old at time of index) with  $\geq 1$  diagnosis for asthma (ICD-9 493.xx) in the pre-index period and continuously eligible to receive healthcare services for 1-year pre-index and at least 60 days post-index. Patients were excluded if they had  $\geq 1$  Rx claim for any asthma controller in the pre-index period. MON subjects were propensity score matched 2:1 to FP44 based on age, gender, region, season of index, specialist (y/n), rhinitis diagnosis, ED/IP visits, mean albuterol and/or OCS use. Exacerbations (ED/IP visits) were compared across the cohorts and cox proportional hazards regression analysis compared time to asthma related event. Predicted monthly total

asthma costs were estimated using a generalized linear model with a gamma distribution and log link. All statistical models adjusted for age, pre-period mean SABA canisters, mean OCS use, and costs. Results: 19,178 subjects were identified (2,294 FP44 and 16,884 MON). After matching, there were 6636 children (34.6%) with 2212 FP44 and 4424 MON use. Mean age was 7.2 ( $\pm$ 2.2) years and 40.6% female for both cohorts. Asthma-related ED/IP visits, 7.8% vs 8.4%, and mean albuterol canisters, 1.29 (1.15) vs 1.21 (1.61), were similar at baseline for FP44 and MON respectively. The use of low dose FP44 was associated with a 29% lower risk of having an asthma-related ED event (HR 0.706, 95% CI 0.519-0.961) and 25% lower risk of having an asthma-related ED/IP visit (HR 0.751, 95% CI 0.565 - 0.999). In addition, FP44 was associated with \$28 (-\$27, -\$29) lower predicted monthly asthma related costs compared to MON. Conclusion: In asthma patients aged 4-11 years, the use of FP44 was associated with lower risk of asthma related events and lower costs compared to the use of MON in a managed care population.

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## **Oregon Medicaid Drug Class Review: Controller Medications for Asthma Studies for *Advair***

This response may include reference to information about *Advair Diskus*® (fluticasone propionate and salmeterol inhalation powder); *Advair HFA*® (fluticasone propionate and salmeterol) Inhalation Aerosol.

- As part of the public comment process, the following abstracts and citations for *Advair* listed below have been identified for possible inclusion. The citations/abstracts were identified by searching Embase for the time period of March 2010 to the present date. The search terms included; clinical trial, efficacy, safety, safe, fluticasone propionate, salmeterol, fluticasone plus salmeterol. The studies were included based on the principles of evidence-based medicine and, therefore, references may not be all-inclusive.
- *Advair HFA* is not indicated for use in children less than 12 years of age.
- Important safety information is found in the attached Prescribing Information.
- The prescribing information for this product contains a boxed warning. Please consult the WARNING section of the attached prescribing information for further details and for important safety information.

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### **Safety and efficacy of long-term treatment with fluticasone propionate and salmeterol via DISKUS versus fluticasone propionate alone**

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FSC 250/50 mcg improved AM PEF and increased the percentage of symptom-free days. The asthma attack rate was similar between treatments, as was the safety profile. FSC 250/50 mcg demonstrated improvements in lung function and asthma control vs FP 250 mcg, although statistically significant differences were not consistent. The differences may be representative of this population with less severe disease at entry. In patients with mild-to-moderate persistent asthma FSC offers improved parameters of asthma control compared with ICS alone. © 2011 Informa Healthcare USA, Inc. Copyright

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### **Fluticasone propionate-salmeterol versus inhaled corticosteroids plus montelukast: Outcomes study in pediatric patients with asthma**

**Stanford R.H., Shah M. and D'Souza A.O.**  
**Journal of Asthma and Allergy 2013 :6 (1-10)**

Background: The purpose of this study (GSK ADA111194) was to compare asthma-related health care utilization and costs associated with fluticasone propionate (an inhaled corticosteroid [ICS]) and salmeterol (a long-acting beta-agonist) in a single inhalation device (fluticasone propionate-salmeterol) versus the combination of ICS + montelukast in the treatment of pediatric patients with asthma. Methods: This was a retrospective, observational cohort study using a large health insurance claims database spanning January 1, 2000 to January 31, 2008. The target population was patients aged 4-11 years with at least one pharmacy claim for fluticasone propionate-salmeterol, any ICS, or montelukast during the study period. The date of first claim for the medication of interest was deemed the index date. Patients were required to be continuously eligible to receive health care services one year prior to and 30 days after the index date, and have at least one claim with an ICD-9-CM code for asthma (493.xx) in the one-year pre-index period. Patients with prescriptions for fluticasone propionate-salmeterol, ICS + montelukast, or long-acting beta-agonists during the pre-index period were excluded. Patients were matched on a 1:1 basis according to three variables, ie, pre-index use of oral corticosteroids, ICS, and presence of pre-index respirator related hospitalizations/emergency department visits. The risk of asthma-related hospitalization, combined hospitalization/emergency department visit, and monthly asthma-related costs were assessed using multivariate methods. Results: Of the 3001 patients identified, 2231 patients were on fluticasone propionate-salmeterol and 770 were on ICS + montelukast. After matching, there were 747 pairs of fluticasone propionate-salmeterol and ICS + montelukast patients, which were well matched for baseline characteristics. Patients who started fluticasone propionate-salmeterol compared with patients on ICS + montelukast had a significantly ( $P < 0.02$ ) lower rate of asthma-related hospitalizations (0.3% versus 3.5%) and asthma-related hospitalizations/emergency department visits (3.5% versus 5.7%). After controlling for baseline and patient characteristics, fluticasone propionate salmeterol users were associated with a significantly lower risk of an asthma-related hospitalization (adjusted hazard ratio 0.039; 95% confidence interval 0.004-0.408) or hospitalization/emergency department visit (hazard ratio 0.441; 95% confidence interval 0.225-0.864), and \$151 (95% confidence interval

67-346) lower asthma-related monthly costs compared with ICS + montelukast. Conclusion: In patients aged 4-11 years with asthma, use of fluticasone propionate-salmeterol was associated with lower asthma-related health care utilization and costs compared with use of ICS + montelukast.

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### **Effect of switching from salmeterol/fluticasone to formoterol/budesonide combinations in patients with uncontrolled asthma**

**Akamatsu T., Shirai T., Kato M., Hashimoto D., Yasui H., Inui N., Suda T., Yokomura K., Hayakawa H., Ide K., Toyoshima M., Kuroishi S., Yasuda K., Suganuma H., Yamada T., Masuda M. and Chida K. *Allergy International* 2012 61:2 (323-329)**

Background: Combination therapy with an inhaled corticosteroid (ICS) and a long-acting  $\beta_2$ -agonist (LABA) in a single inhaler is the mainstay of asthma management and salmeterol/fluticasone combination (SFC) and fixed-dose formoterol/budesonide combination (FBC) are currently available in Japan; however, there is nothing to choose between the two. The purpose of this study was to clarify the effect of switching from SFC to FBC in patients with asthma not adequately controlled under the former treatment regimen. Method: This was a prospective, multicenter, open-label, uncontrolled longitudinal study in 87 adult patients with an Asthma Control Questionnaire, 5-item version (ACQ5) score of greater than 0.75 under treatment with SFC 50/250  $\mu\text{g}$  one inhalation twice daily (bid). SFC was switched to FBC 4.5/160  $\mu\text{g}$  two inhalations bid. Study outcomes included ACQ5 score, peak expiratory flow (PEF), FEV1, and fractional exhaled nitric oxide (FeNO) at the end of treatment period. Results: Eighty-three patients completed the study. ACQ5 scores improved and exceeded the clinically meaningful difference after 12 weeks of treatment and well-controlled asthma (ACQ5 score  $\leq 0.75$ ) was attained in 37 (44.6%) patients. Minimum and maximum PEF and FEV1 values improved significantly, but not FeNO values, after switching from SFC to FBC. Conclusions: Switching ICS/LABA combination therapy is a useful option in the management of asthma that is not optimally controlled. ©2012 Japanese Society of Allergology. Copyright

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### **Efficacy and tolerability of salmeterol/fluticasone propionate versus fluticasone propionate in asthma patients: A randomized, double-blind study**

**Lee Y.-S., Lin H.-C., Huang C.-D., Lee K.-Y., Liu C.-Y., Yu C.-T., Wang C.-H. and Kuo H.-P.**



**Chang Gung Medical Journal 2011 34:4 (382-394)**

Background: A combination of salmeterol and fluticasone propionate (SAL/FP) has been shown to be effective in the treatment of asthma. We compared the efficacy and tolerability of SAL/FP (50/250 µg) with fluticasone propionate (FP) 250 µg administered twice daily for 2 weeks in treating patients with mild to moderate asthma. Methods: This was a randomized, double-blind study in adult patients with symptomatic asthma that was not controlled by 1000 µg/d inhaled corticosteroids (ICS) alone. 48 asthmatics were randomized to receive 2 inhalations of SAL/FP 50/250 µg bis in die (BID) or 2 inhalations of FP 250 µg BID, both delivered via Accuhaler device, for 2 weeks. The primary objective was the mean change from baseline in the mean morning peak expiratory flow (PEF) over the two week period. Other parameters included lung function, daily asthma symptom scores, evening PEF, percentage of days free of rescue medication use and daily rescue medication use. Tolerability was assessed by adverse events spontaneously elicited at clinic visits. Results: 46 patients provided evaluable efficacy for analysis. The morning PEF improved significantly throughout the two weeks of treatment compared with baseline in the SAL/FP group. Mean morning PEF was 23.0 L/min higher in SAL/FP group than in FP group ( $p = 0.013$ ). The change of forced expiratory volume in one second (FEV1) from baseline was greater in SAL/FP group compared to FP group ( $p = 0.048$ ). There were similar effects on day-time and night-time symptom scores, percentage symptom free days and nights and usage of salbutamol. 70.8% of the patients receiving SAL/FP were satisfied with the treatment, while only 26.1% of patients receiving FP alone were ( $p = 0.020$ ). No death or acute exacerbation occurred. Conclusion: SAL/FP 50/250 µg was safe and effective, and had a high level of patient satisfaction resulting in significantly greater increases in morning PEF and FEV1 compared to the use of FP 250 µg alone.

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**Combination therapy salmeterol/fluticasone versus doubling dose of fluticasone in children with asthma**

**Mahr T.A. and Mumm J.**

**Pediatrics 2011 128:SUPPL. 3 (S129-S130)**

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**Fluticasone/formoterol combination therapy is as effective as fluticasone/salmeterol in the treatment of asthma, but has a more rapid onset of action: An open-label, randomized study**

**Bodzenta-Lukaszyk A., Dymek A., McAulay K. and Mansikka**

**H. BMC Pulmonary Medicine 2011 11 Article Number 28**

**Background:** The inhaled corticosteroid (ICS) fluticasone propionate (fluticasone) and the long-acting  $\beta$ 2-agonist (LABA) formoterol fumarate (formoterol) are being made available as a combination product (fluticasone/formoterol, flutiform®) in a single aerosol inhaler. This 12-week, open-label, randomized, active-controlled, parallel-group, multicentre, phase 3 study compared the efficacy and safety of fluticasone/formoterol with the commercially available combination product fluticasone/salmeterol. **Methods:** Patients aged  $\geq 18$  years (N = 202) with mild-to-moderate-severe, persistent asthma for  $\geq 6$  months prior to screening were included in the study. After a screening phase (4-10 days), eligible patients were randomized 1:1 to receive fluticasone/formoterol or fluticasone/salmeterol during the 12-week treatment period. The primary objective was to demonstrate non-inferiority of fluticasone/formoterol versus fluticasone/salmeterol, measured by pre-dose forced expiratory volume in the first second (FEV1), at week 12. **Results:** Fluticasone/formoterol was comparable to fluticasone/salmeterol for the primary efficacy endpoint, mean pre-dose FEV1 at week 12. The new combination was also comparable to fluticasone/salmeterol for change from baseline to week 12 in pre-dose FEV1, change from pre-dose FEV1 at baseline to 2-hour post-dose FEV1 at week 12 and discontinuations due to lack of efficacy. Importantly, fluticasone/formoterol was superior to fluticasone/salmeterol in time to onset of action throughout the duration of the study. The two treatments demonstrated similar results for various other secondary efficacy parameters, including other lung function tests, patient-reported outcomes, rescue medication use, asthma exacerbations and Asthma Quality of Life Questionnaire scores. Fluticasone/formoterol was well tolerated and had a good safety profile that was similar to fluticasone/salmeterol. **Conclusions:** The results of this study indicate that fluticasone/formoterol is as effective as fluticasone/salmeterol, and has a more rapid onset of action, reflecting the faster bronchodilatory effects of formoterol compared with those of salmeterol. If patients perceive the benefits of therapy with fluticasone/formoterol more rapidly than with fluticasone/salmeterol, this could have a positive impact on preference and adherence. **Trial Registration:** ClinicalTrials.gov: NCT00476073. © 2011 Bodzenta-Lukaszyk et al; licensee BioMed Central Ltd. Copyright 2011 Elsevier B.V., All rights reserved.

### **Long-term treatment with fluticasone propionate/salmeterol via Diskus improves asthma control versus fluticasone propionate alone**

**Katial R.K., Bernstein D., Prazma C.M., Lincourt W.R. and Stempel D.A. Allergy and Asthma Proceedings 2011 32:2 (127-136)**

This 52-week study was designed to assess the safety and efficacy of fluticasone propionate/salmeterol combination (FSC) 250/50 micrograms versus fluticasone propionate (FP) 250 micrograms in subjects with persistent asthma symptomatic on open-label FP 100 micrograms. The primary objective of this study was to show that FSC 250/50 micrograms was superior to FP 250 micrograms at increasing pulmonary function as measured by forced expiratory volume in 1 second over a 52-week treatment period. A secondary objective was to compare the rate of asthma attacks defined as (1) a sustained 2-day decrease in morning peak expiratory flow or increase in albuterol use for 2 consecutive days, (2) an asthma exacerbation requiring systemic corticosteroids, or (3) an unscheduled clinic or hospital visit for acute

asthma symptoms. Three hundred six subjects received FSC 250/50 micrograms and 315 subjects received FP 250 micrograms. Both treatments were administered twice daily. Treatment with FSC 250/50 micrograms resulted in a significant improvement in lung function compared with FP 250 micrograms ( $p < 0.001$ ). Additionally, treatment with FSC 250/50 micrograms resulted in a reduction in the rate of exacerbations of asthma (i.e., requiring systemic corticosteroids or unscheduled urgent care intervention) compared with FP 250 micrograms (0.170 versus 0.273, respectively;  $p = 0.017$ ). There was no differentiation between treatments for less severe attacks of asthma. FSC 250/50 micrograms showed consistently greater improvement in lung function, symptom control, and decreased albuterol use. In addition, FSC 250/50 micrograms - treated subjects experienced fewer severe asthma exacerbations than subjects treated with FP 250 micrograms.

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### **Comparison of the effect of low-dose ciclesonide and fixed-dose fluticasone propionate and salmeterol combination on long-term asthma control**

**Postma D.S., O'Byrne P.M. and Pedersen S. Chest 2011 139:2 (311-318)**

Background: Patients with mild persistent asthma constitute about 70% of the asthma population; thus, it is important to know which first-line treatment is best for the management of mild asthma. We compared benefits of first-line treatment with ciclesonide and a combination of fluticasone and salmeterol in patients with mild asthma. Methods: Patients aged 12 to 75 years with mild persistent asthma were enrolled in a randomized, double-blind, placebo- controlled study. After run-in, patients were randomized to ciclesonide 160 µg once daily (CIC160), fluticasone propionate/salmeterol 100/50 µg bid (FP200/S100), or placebo for 52 weeks. The primary variable was time to first severe asthma exacerbation; the coprimary variable was the percentage of poorly controlled asthma days. Patients recorded asthma symptoms and salbutamol use in electronic diaries and completed a standardized version of the Asthma Quality of Life Questionnaire. Results: Compared with placebo, the time to first severe asthma exacerbation was prolonged, and lung function was improved with FP200/S100 treatment ( $P = .0002$ ) but not with CIC160. Both CIC160 and FP200/S100 provided significantly fewer poorly controlled asthma days than placebo ( $P \leq .0016$  for both active treatments). Moreover, both active treatments provided significantly more asthma symptom-free days ( $P \leq .0001$ ), rescue medication-free days ( $P = .0005$ , one-sided), and days with asthma control ( $P \leq .0033$ ). Overall Asthma Quality of Life Questionnaire scores were significantly higher in both active treatment groups than placebo ( $P \leq .0017$ ). Conclusions: In mild asthma, FP200/S100 prolonged time to first severe asthma exacerbation, and CIC160 and FP200/S100 were clinically equieffective for most measures of asthma control. © 2011 American College of Chest Physicians.

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## **Combination therapy salmeterol/fluticasone versus doubling dose of fluticasone in children with asthma**

**Vaessen-Verberne A.A.P.H., Van Den Berg N.J., Van Nierop J.C., Brackel H.J.L., Gerrits G.P.J.M., Hop W.C.J. and Duiverman E.J.**  
**American Journal of Respiratory and Critical Care Medicine 2010 182:10 (1221-1227)**

Rationale: For children with symptomatic asthma despite low to moderate doses of inhaled corticosteroids, evidence is still lacking whether to add a long-acting bronchodilator or to increase the dose of inhaled corticosteroids. Objective: To evaluate whether salmeterol/fluticasone propionate (SFP), 50/100 µg twice a day, is non inferior regarding symptom control compared with fluticasone propionate (FP), 200 µg twice a day Diskus in children with symptomatic asthma. Methods: A multicenter, randomized, parallel-group, double-blind study was performed comparing SFP and FP treatment during 26 weeks on asthma control and lung function. Measurements and Main Results: A total of 158 children, 6-16 years old, still symptomatic on FP, 100 µg twice a day, during a 4-week run in period, were included. Percentage of symptom-free days during the last 10 weeks of the treatment period did not differ between treatment groups (per protocol analysis: adjusted mean difference [FP minus SFP] 2.6%; 95% confidence interval, -8.1 to 13.4). Both groups showed substantial improvements of about 25 percent points in symptom-free days (both P < 0.001 from baseline). Lung function measurements (FEV1, FVC, PEF rate, and maximal expiratory flow) did not differ between groups except for a slight advantage in maximal expiratory flow in the SFP group at 1 week. No differences were found between FP and SFP regarding exacerbation rates, adverse events, or growth. Conclusions: In our study the efficacy on symptom control and lung function of the combination of a long-acting bronchodilator with inhaled corticosteroid is equal to doubling the dose of the inhaled corticosteroid in children still symptomatic on a moderate dose of inhaled corticosteroid. Clinical trial registered with [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT 00197106).

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## **Effect of salmeterol/fluticasone propionate combination on airway hyper-responsiveness in patients with well-controlled asthma**

**Chanez P., Stallaert R., Reznikova E., Bloemen P., Adamek L. and Joos G. Respiratory Medicine 2010 104:8 (1101-1109)**

Background: The hypothesis that regular treatment aimed at achieving and maintaining asthma control is accompanied by reduced airway hyper-responsiveness (AHR) was investigated. Methods: Adult patients (PC20 methacholine <8 mg/ml, FEV1% predicted ≥70%) received salmeterol/fluticasone propionate combination 50/250 µg bd (SFC250) for a 12-week run-in; those achieving well-controlled (WC) asthma were randomised to SFC250 (n

= 88) or SFC50/500 µg bd (SFC500) (n = 90) for 24 weeks. AHR (PC20 methacholine), asthma control, lung function, symptoms, exacerbations and safety were assessed. Results: During the 12 week run-in (SFC250), a greater than 1 doubling dose increase in PC20 was observed. During randomised treatment, the increase in AHR was similar, and less than 1 doubling dose, for both groups (adjusted geometric mean PC20 (mg/mL) at 24 weeks: SFC250: 2.796, SFC500: 2.802; p = 0.992). Compared with SFC250, patients receiving SFC500 had a more rapid improvement in AHR (adjusted mean ratio to baseline respectively at week 4: 1.193 vs. 1.386; week 12: 1.395 vs. 1.672; p = non-significant for both) and showed a greater response to treatment in patients with a low baseline PC20. Patients maintaining WC asthma were 72 (84%) and 64 (74%) in the SFC250 and SFC500 groups respectively. Both doses of SFC were well tolerated; only four exacerbations were reported, all in the SFC500 group. Conclusion: Regular treatment with SFC resulted in continuous improvement in AHR with maintenance of asthma control in the majority of patients. SFC500 showed a trend for a more rapid improvement in AHR and resulted in greater improvements in patients with a lower baseline PC20.

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### **Treatment comparison of budesonide/formoterol with salmeterol/fluticasone propionate in adults aged ≥16 years with asthma: Post hoc analysis of a randomized, double-blind study**

**Kuna P.**  
**Clinical Drug Investigation 2010 30:9 (565-579)**

Background: Three fixed maintenance-dose inhaled corticosteroid/long-acting b2-agonist (ICS/LABA) combinations for the treatment of asthma are currently available: salmeterol/fluticasone propionate (Seretide™/Advair™/ Adoair™) budesonide/formoterol (Symbicort®) and beclometasone/ formoterol (Foster™). All of these combinations have proven efficacy in terms of controlling symptoms, improving lung function and reducing the rate of exacerbations compared with ICSs and LABAs administered separately. Budesonide/formoterol is also approved for use as maintenance and reliever therapy in a number of countries (Symbicort SMART®). Many of the studies supporting the use of budesonide/formoterol combination therapies have included populations of adolescents and adults aged > 11 years. Objective: This post hoc analysis compared the efficacy of ICS/LABA fixed maintenance-dose treatment with budesonide/formoterol and salmeterol/ fluticasone propionate versus budesonide/formoterol maintenance and reliever therapy in patients with persistent asthma aged ≥16 years. Methods: Following 2-weeks run-in, 2866 adults aged ≥16 years were randomized to: fixed maintenance- dose budesonide/formoterol 640 µg/18 µg per day, salmeterol/fluticasone propionate 100 µg/500 µg per day plus terbutaline as needed, or budesonide/formoterol 320 µg/9 mg per day plus additional inhalations as needed (budesonide/formoterol maintenance and reliever therapy). Outcome measures included time to

first severe asthma exacerbation (primary outcome) and number of severe asthma exacerbations. Results: Budesonide/formoterol maintenance and reliever therapy prolonged time to first severe exacerbation versus budesonide/formoterol and salmeterol/fluticasone propionate fixed maintenance dose ( $p = 0.037$  and  $p = 0.0089$ , respectively). Compared with salmeterol/fluticasone propionate fixed maintenance-dose treatment, fixed maintenance-dose budesonide/ formoterol reduced the risk of hospitalizations/ emergency-room visits by 28% (relative rate [RR] 0.72; 95% CI 0.53, 0.98;  $p = 0.034$ ) and budesonide/ formoterol maintenance and reliever therapy by 37% (RR 0.63; 95% CI 0.46, 0.87;  $p = 0.0043$ ). All treatments provided similar improvements in lung function, asthma control days and asthma-related quality of life. Conclusions: Budesonide/formoterol fixed maintenance dose or maintenance and reliever therapy provides similar improvements in current asthma control and reduces the future risk of hospitalizations/emergency-room treatments versus salmeterol/fluticasone propionate fixed maintenance-dose treatment, providing additional clinical benefit to asthma patients aged  $\geq 16$  years.  
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### **Meta-analysis of serious asthma-related outcomes in subjects receiving advair**

**Knobil K., Yancey S., Kral K. and Sutton L.**

**Journal of Allergy and Clinical Immunology 2010 125:2 SUPPL. 1 (AB70)**

**RATIONALE:** Evidence-based asthma guidelines recommend adding a LABA as preferred therapy in adults and children uncontrolled on ICS alone. The guidelines also state that for asthma, a LABA should always be used concurrently with ICS. **METHODS:** A meta-analysis of 215 studies evaluating salmeterol (n=5106,575) was performed. SAE reports were independently adjudicated by external physicians to determine the outcomes of interest: asthma-related deaths, intubations and hospitalizations. Risk differences per 10,000 patients and associated 95% CIs were calculated. As salmeterol should be used concurrently with ICS, results for Advair $\geq$  vs. ICS alone are reported. Additional information about the meta-analysis can be found on the FDA website at: <http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4398b1-04-GSK.pdf>. **RESULTS:** 22,600 subjects from 63 studies, representing 10,028 patient years of exposure for Advair vs. ICS were included. There were no asthma related deaths or intubations in subjects receiving Advair. In the total population, there were 31 subjects with an asthma-related hospitalization receiving Advair and 29 for ICS alone; RD50.28 per 10,000 patients (-18.51, 19.06). For pediatric subjects (4-11 years; n=2478), a sub-set of the total population, there was 1 asthma-related hospitalization in a subject receiving Advair and 2 subjects with a hospitalization for ICS alone; RD5-5.39 per 10,000 patients (-60.34, 49.57). **CONCLUSIONS:** When appropriate use of salmeterol and ICS was assured (in a single device as Advair) there appeared to be no increased risk of asthma-related events. These data and the well-documented efficacy of Advair affirm the recommended position of ICS plus LABA therapy as a preferred therapeutic option for patients not controlled on ICS alone (GSK-funded). Copyright 2010 Elsevier B.V., All rights reserved.

**Incidence of oral candidiasis among patients with asthma receiving fluticasone propionate/salmeterol dry powder inhaler versus beclomethasone dipropionate hydrofluoroalkane: Large-scale retrospective claims analysis**

**Peters S.P., Benninger M., Hankin C.S., Wang Z., Bronstone A., Buck P. and Lepore M.S. Journal of Allergy and Clinical Immunology 2013 131:2 SUPPL. 1 (AB2)**

**RATIONALE:** Oral candidiasis (OC) associated with inhaled corticosteroid (ICS) administration may arise as a result of oropharyngeal deposition of ICS and can be related to ICS dose, delivery system, inhalation technique, and ICS particle size. This analysis examined database prescription claims to compare OC rates associated with fluticasone propionate/salmeterol dry powder inhaler (FP/SAL-DPI; median particle [MMAD] size of 3 mm) versus beclomethasone dipropionate hydro-fluoroalkane (BDP-HFA; extra-fine MMAD particle size of 1 mm). We hypothesized that the small particle ICS formulation would be associated with a lower rate of OC. **METHODS:** Five-year (1/1/2006-12/31/2010) MarketScan Commercial and Medicare Supplemental databases identified patients diagnosed with asthma,  $\geq 12$  years old, newly prescribed an ICS ( $\geq 1$  year of data before first fill), with  $\geq 1$  year follow-up. Patients receiving antibiotics/oral corticosteroids (within 1 month), radiation/chemotherapy (within 3 months), or having an immunodeficiency diagnoses (within 6 months) before OC diagnosis were excluded. Logistic regression was performed for OC rate by treatment (FP/SAL- DPI versus BDP-HFA) adjusted for age, sex, region, employment, and comorbidities (COPD, emphysema, chronic, diabetes, allergic rhinitis, allergic conjunctivitis, and atopic dermatitis). **RESULTS:** Among 39,924 patients, 26,977 received FP/SAL-DPI and 12,947 BDP-HFA. Adjusting for demographics and comorbidities, patients receiving FP/SAL-DPI were 1.17 times more likely to subsequently develop OC than patients receiving BDP-HFA (95% CI 1.02-1.33,  $p=0.02$ ). **CONCLUSIONS:** In this real-world analysis of a large retrospective claims database, patients with asthma who received FP/SAL-DPI had a significantly higher likelihood of subsequent OC than those who received BDP-HFA, which could be related, in part, to a larger particle size.

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**Effect of combination fluticasone propionate and salmeterol or inhaled corticosteroids on asthma-related outcomes in a medicare-eligible population**

**Stanford R.H., Blanchette C.M., Roberts M.H., Petersen H. and Fuhlbrigge A.L. American Journal of Geriatric Pharmacotherapy 2012 10:6 (343-351)**

**Background:** National asthma treatment guidelines recommend either the use of inhaled corticosteroids (ICS) or ICS in combination with a long-acting bronchodilator for the treatment of moderate to severe asthma. Even though asthma is common among older adults, few studies

have assessed the differences in effectiveness between these two recommended therapies in patients over 65 years of age. Objective: The aim of this study was to assess the association of the fluticasone-salmeterol combination (FSC) or ICS initiation on asthma-related events in Medicare-eligible asthma patients. Methods: This was a retrospective observational study using a large health claims database (July 1, 2001 to June 30, 2008). Subjects 65 to 79 years of age with 12-month pre-index and 3- to 12-month post-index eligibility, an asthma diagnosis (ICD- 493.xx), and with 1 or more FSC or ICS claims at index were included. Subjects with an FSC or ICS claim in the pre-index and any claim for chronic obstructive pulmonary disease were excluded. Subjects were observed until they had an event (emergency department [ED] inpatient hospitalization [IP], combined IP/ED or oral corticosteroid [OCS] use) or were no longer eligible in the database, whichever came first. Cox proportional hazards regression was used to assess risk of an asthma-related event (IP, ED, or IP/ED). Baseline characteristics (age, sex, region, index season, co-morbidities, pre-index use of short-acting  $\beta$ -agonists, OCS, other asthma controllers, and asthma-related ED/IP visits) were independent covariates in the model. Results: A total of 10,837 met the criteria (4843 ICS and 5994 FSC). Age (70.4 and 70.5 years, respectively) and the percentage of female subjects (65.5% and 64.8%, respectively) were similar. Asthma-related events were also similar at baseline. Post-index unadjusted rates occurring after >30 days were ED (1.8% vs 1.5%,  $P = 0.18$ ), IP (2.7% vs 1.7%,  $P < 0.001$ ), and ED/IP (4.1% vs 2.8%,  $P < 0.001$ ) for ICS and FSC, respectively. Subjects who received FSC were associated with a 32% (adjusted HR = 0.68; 95% CI, 0.51-0.91) lower risk of experiencing an IP visit and a 22% (HR = 0.78; 95% CI, 0.62-0.98) lower risk of experiencing an ED/IP visit. No differences were observed for ED visits (HR = 0.94; 95% CI, 0.68-1.29). Conclusions: In Medicare-eligible asthma patients, FSC use was associated with lower rates of asthma-related serious exacerbations compared with ICS.

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**Efficacy comparison of mometasone furoate/formoterol versus fluticasone propionate/salmeterol combination therapies in subjects with persistent asthma: Noninferiority and onset-of-action findings**

**Bernstein D., Murphy K. and Nolte H.**  
**World Allergy Organization Journal 2012 5 SUPPL. 2 (S79)**

Background: Mometasone furoate/formoterol (MF/F) combination therapy is a new treatment recently approved by the US Food and Drug Administration for the treatment of persistent asthma and currently under regulatory review by Canadian authorities. We report findings from a non-inferiority study that compared effects of MF/F and fluticasone propionate/salmeterol (FP/S) combination therapies on pulmonary function and onset of action in subjects with persistent asthma. Methods: This randomized, active-controlled, multicenter, non-inferiority trial enrolled subjects (aged  $\geq 12$  years) previously treated with medium-dose inhaled corticosteroid alone or combined with a long-acting  $\beta_2$ -agonist. Following a 2- to 4-



week run-in treatment period with MF administered via a metered-dose inhaler (MDI) 200 mg twice daily (BID), eligible subjects were randomized to MF/F-MDI 200/10 mg BID or FP/S administered via a dry powder inhaler (DPI) 250/50 mg BID for 12 weeks. The primary endpoint of this trial was change from baseline in area under the curve (AUC) in forced expiratory volume in 1 second (FEV1) measured serially for 0 to 12 hours post dose (FEV1 AUC0-12h). Key secondary endpoints included onset of action, defined as change from baseline in FEV1 at 5 minutes post dose on day 1. Results: 722 subjects were randomized to MF/F-MDI (n = 371) or FP/S-DPI (n = 351). The trial's primary endpoint was met, demonstrating that MF/F administered via an MDI was non-inferior to FP/S administered via a DPI in the patient population investigated. Mean FEV1 AUC0-12h at endpoint for MF/F-MDI and FP/S-DPI was 3.43 versus 3.24 L × h, respectively (95% CI, -0.40 to 0.76). Analysis of onset-of-action characteristics revealed that MF/F's effect on lung function occurred significantly faster than the effect observed with FP/S- DPI. MF/F-MDI was associated with a 200-mL mean increase from baseline in FEV1 at 5 minutes post dose (first scheduled measurement) on the first day of treatment vs. a 90-mL increase for FP/S-DPI (P < 0.001). Conclusions: This trial demonstrated that MF/F 200/10 mg BID administered via an MDI was non-inferior to FP/S 250/50 mg BID administered via a DPI in its effect to improve lung function as measured by FEV1 AUC0-12h. However, the onset of action for this effect was significantly faster with MF/F-MDI than with FP/S-DPI.

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### **Efficacy and onset of action of mometasone furoate/formoterol and fluticasone propionate/salmeterol combination treatment in subjects with persistent asthma**

**Bernstein D.I., Hébert J., Cheema A., Murphy K.R., Chérrez-Ojeda I., Matiz-Bueno C.E., Kuo W.-L. and Nolte H.**

**Allergy, Asthma and Clinical Immunology 2011 7:1 Article Number 21**

Background: Mometasone furoate/formoterol (MF/F) is a novel combination therapy for treatment of persistent asthma. This non-inferiority trial compared the effects of MF/F and fluticasone propionate/salmeterol (FP/S) combination therapies on pulmonary function and onset of action in subjects with persistent asthma. Methods: Following a 2- to 4-week run-in period with MF administered via a metered-dose inhaler (MDI) 200 µg (delivered as 2 inhalations of MF-MDI 100 µg) twice daily (BID), subjects (aged ≥12 y) were randomized to MF/F-MDI 200/10 µg BID (delivered as 2 inhalations of MF/F-MDI 100/5 µg) or FP/S administered via a dry powder inhaler (DPI) 250/50 µg (delivered as 1 inhalation) BID for 12 weeks. The primary assessment was change from baseline to week 12 in area under the curve for forced expiratory volume in 1 second measured serially for 0-12 hours post dose (FEV1 AUC 0-12 h). Secondary assessments included onset of action (change from baseline in FEV1 at 5 minutes post dose on day 1) and patient-reported outcomes. Results: 722 subjects were randomized to MF/F-MDI (n = 371) or FP/S-DPI (n = 351). Mean FEV1 AUC0-12 h change from baseline at week 12 for MF/F-MDI and FP/S-DPI was 3.43 and 3.24 L × h, respectively (95% CI, -0.40 to 0.76). MF/F-MDI was associated with a 200-mL mean increase from

baseline in FEV1 at 5 minutes post dose on day 1, which was significantly larger than the 90-mL increase for FP/S-DPI ( $P < 0.001$ ). The overall incidence of adverse events during the 12-week treatment period that were considered related to study therapy was similar in both groups (MF/F-MDI, 7.8% [n = 29]; FP/S-DPI, 8.3% [n = 29]). Conclusions: The results of this 12-week study indicated that MF/F improves pulmonary function and asthma control similar to FP/S with a superior onset of action compared with FP/S. Both drugs were safe, improved asthma control, and demonstrated similar results for other secondary study endpoints.

Trial registration: ClinicalTrials.gov: NCT00424008. © 2011 Bernstein et al; licensee BioMed Central Ltd.

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### **Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children.**

**Lasserson T.J., Ferrara G. and Casali L.**

**Cochrane database of systematic reviews (Online) 2011 12 (CD004106)**

Long-acting beta-agonists are a common second line treatment in people with asthma inadequately controlled with inhaled corticosteroids. Single device inhalers combine a long-acting beta-agonist with an inhaled steroid delivering both drugs as a maintenance treatment regimen. This updated review compares two fixed-dose options, fluticasone/salmeterol FP/SAL and budesonide/formoterol, since this comparison represents a common therapeutic choice. To assess the relative effects of fluticasone/salmeterol and budesonide/formoterol in people with asthma. We searched the Cochrane Airways Group register of trials with pre-specified terms. We performed additional hand searching of manufacturers' web sites and online trial registries. Search results are current to June 2011. We included randomised studies comparing fixed dose fluticasone/salmeterol and budesonide/formoterol in adults or children with a diagnosis of asthma. Treatment in the studies had to last for a minimum of 12 weeks. Two authors independently assessed studies for inclusion in the review. We combined continuous data outcomes with a mean difference (MD), and dichotomous data outcomes with an odds ratio (OR). We assessed the quality of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. Five studies met the review entry criteria (5537 adults). Study populations entered the studies having previously been treated with inhaled steroids and had moderate or mild airway obstruction (mean FEV(1) predicted between 65% and 84% at baseline). Most of the studies assessed treatment over a period of six months. The studies were at a low risk of selection and performance/detection bias, although we could not determine whether missing data had an impact on the results. Availability of outcome data was satisfactory. Primary outcomes the odds ratio for exacerbations requiring oral steroids was lower with fluticasone/salmeterol but did not reach statistical significance (OR 0.89, 95% confidence interval (CI) 0.74 to 1.07, four studies, N = 4949). With an assumed risk with budesonide/formoterol of 106/1000 participants requiring oral steroids, treatment with fluticasone/salmeterol would lead to between 25 fewer and seven more people per 1000 experiencing a course of oral steroids. Although the odds of

hospital admission were higher with fluticasone/salmeterol, this did not reach statistical significance (OR 1.29, 95% CI 0.68 to 2.47, four studies, 4879 participants). With an assumed risk in the budesonide/formoterol of 7/1000, between two fewer and 10 more people per 1000 would be hospitalised on fluticasone/salmeterol. The odds of a serious adverse event related to asthma was higher with fluticasone/salmeterol but did not differ significantly between treatments (OR 1.47, 95% CI 0.75 to 2.86, three studies, 4054 participants). With an assumed risk in the budesonide/formoterol of 7/1000, between two fewer and 13 more people per 1000 would experience a serious adverse event on fluticasone/salmeterol. Secondary outcomes lung function outcomes, symptoms, rescue medication, composite of exacerbations leading to either emergency department visit or hospital admission, withdrawals and adverse events did not differ statistically between treatments. Assessment of quality of life was limited to two studies, both of which gave results that did not reach statistical significance. One study reported one death out of 1000 participants on fluticasone/salmeterol and no deaths in a similar number of participants treated with budesonide/formoterol. No deaths were reported in the other studies. Statistical imprecision in the effect estimates for exacerbations and serious adverse events do not enable us to conclude that either therapy is superior. The uncertainty around the effect estimates justify further trials to provide more definitive conclusions; the overall quality of evidence based on GRADE recommendations for the three primary outcomes and withdrawals due to serious adverse events was moderate. We rated the quality of evidence for mortality to be low. Results for lung function outcomes showed that the drugs were sufficiently similar that further research is unlikely to change the effects. No trials were identified in the under-12s and research in this population is a high priority. Evaluation of quality of life is a priority for future research.

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**Fluticasone/formoterol combination therapy is as effective as fluticasone/salmeterol in the treatment of asthma, but has a more rapid onset of action: an open-label, randomized study.**

**Bodzenta-Lukaszyk A., Dymek A., McAulay K. and Mansikka H. BMC pulmonary medicine 2011 11 (28)**

The inhaled corticosteroid (ICS) fluticasone propionate (fluticasone) and the long-acting  $\beta$ 2-agonist (LABA) formoterol fumarate (formoterol) are being made available as a combination product (fluticasone/formoterol, flutiform®) in a single aerosol inhaler. This 12-week, open-label, randomized, active-controlled, parallel-group, multicentre, phase 3 study compared the efficacy and safety of fluticasone/formoterol with the commercially available combination product fluticasone/salmeterol. Patients aged  $\geq 18$  years (N = 202) with mild-to-moderate-severe, persistent asthma for  $\geq 6$  months prior to screening were included in the study. After a screening phase (4-10 days), eligible patients were randomized 1:1 to receive fluticasone/formoterol or fluticasone/salmeterol during the 12-week treatment period. The primary objective was to demonstrate non-inferiority of fluticasone/formoterol versus fluticasone/salmeterol, measured by pre-dose forced expiratory volume in the first second

(FEV1), at week 12. Fluticasone/formoterol was comparable to fluticasone/salmeterol for the primary efficacy endpoint, mean pre-dose FEV1 at week 12. The new combination was also comparable to fluticasone/salmeterol for change from baseline to week 12 in pre-dose FEV1, change from pre-dose FEV1 at baseline to 2-hour post-dose FEV1 at week 12 and discontinuations due to lack of efficacy. Importantly, fluticasone/formoterol was superior to fluticasone/salmeterol in time to onset of action throughout the duration of the study. The two treatments demonstrated similar results for various other secondary efficacy parameters, including other lung function tests, patient-reported outcomes, rescue medication use, asthma exacerbations and Asthma Quality of Life Questionnaire scores. Fluticasone/formoterol was well tolerated and had a good safety profile that was similar to fluticasone/salmeterol. The results of this study indicate that fluticasone/formoterol is as effective as fluticasone/salmeterol, and has a more rapid onset of action, reflecting the faster bronchodilatory effects of formoterol compared with those of salmeterol. If patients perceive the benefits of therapy with fluticasone/formoterol more rapidly than with fluticasone/salmeterol, this could have a positive impact on preference and adherence. Copyright MEDLINE® is the source for the citation and abstract of this record

### **Retrospective comparison of early versus late treatment with fluticasone propionate/salmeterol after an asthma exacerbation**

**Hagiwara M., Delea T.E. and Stanford R.H. Journal of Asthma 2011 48:7 (721-728)**

Background. The benefits of inhaled corticosteroids in asthma are well established. Early use of inhaled anti-inflammatories following an exacerbation could be beneficial. Methods. A retrospective observational cohort study compared the risk of asthma-related exacerbations [hospitalization, emergency department visit, and/or treatment with systemic corticosteroid] in patients receiving treatment with fluticasone propionate/salmeterol in a single inhaler (FSC) within 90 days following an initial asthma-related exacerbation (early treatment) versus patients receiving the treatment subsequently (late treatment). Data were from a large health insurance claims database spanning from January 1998 to April 2008. Subjects included patients with  $\geq 1$  prescription for FSC  $\leq 1$  year after first asthma-related exacerbation. Patients with early treatment were matched to those with late treatment by propensity score and compared in terms of healthcare utilization and costs after initiation of FSC. Results. A total of 14,861 patients met study inclusion criteria, including 10,793 early and 4068 late treatment patients. After matching, 3555 pairs were well matched on all pretreatment characteristics and duration of follow-up (mean 722 vs. 717 days,  $p = .634$ ). Early versus late treatment was associated with longer time to first asthma-related exacerbation (hazard ratio = 0.82, 95% CI 0.75-0.88,  $p < .001$ ), fewer short-acting  $\beta$ -agonists prescriptions (3.3 vs. 3.6,  $p = .031$ ), higher outpatient yearly per patient pharmacy costs (\$1320 vs. \$1163,  $p = .008$ ), and lower yearly per patient asthma-related emergency department visit costs (\$80 vs. \$105,  $p = .032$ ). Total yearly per patient asthma-related costs were similar (\$2197 vs. \$2064,  $p = .203$ ). Conclusions. Earlier use of FSC following an asthma exacerbation was associated with reduced risk of future

asthma-related exacerbation and lower use of rescue medications. © 2011 Informa Healthcare USA, Inc. Copyright

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### **Fluticasone propionate/salmeterol combination in children with asthma: Key cardiac and overall safety results**

**Li J.S., Qaqundah P.Y., Weinstein S.F., Laforce C.F., Ellsworth A.V., Ortega H.G., and Ferro T.J.**  
**Clinical Research and Regulatory Affairs 2010 27:3 (87-95)**

This study studied the safety of fluticasone propionate/salmeterol combination (FSC) 100/50 HFA (2 inhalations of 50/25 mcg) twice daily, compared with fluticasone propionate (FP) 100 HFA (two inhalations of 50 mcg) twice daily, over a 12-week treatment period in subjects aged 4-11 years with persistent asthma. Of the 350 subjects randomized to receive double-blind treatment, 173 received FSC 100/50 HFA and 177 received FP 100 HFA. The two treatment groups were comparable in adverse events profiles, vital signs, asthma exacerbations, oropharyngeal examinations, clinical laboratory tests and urinary cortisol levels. The use of spacer did not meaningfully modify cortisol levels. The pre-specified analysis of 12-lead electrocardiograms (ECGs) identified abnormalities during screening as well as post-randomization in both study treatments, even though randomized subjects were without pre-existing cardiovascular disorders. An ad hoc analysis of the ECG data found no clinically relevant ECG abnormalities either prior to randomization or after randomization to study treatments. Thus, the ECG findings were false-positives related to details of the pre-specified analysis. This study highlights the importance of methodology when interpreting ECG data in a pediatric clinical trial. Overall, both FSC 100/50 HFA and FP 100 HFA were well-tolerated in children aged 4-11 years with persistent asthma. © 2010 Informa Healthcare USA, Inc.

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### **Long-term treatment with fluticasone propionate (FP) and salmeterol via Diskus® (FSC) improves asthma control versus fluticasone propionate (FP) alone**

**Katial R., Bernstein D., Prazma C., Lincourt W. and Stempel D.**  
**American Journal of Respiratory and Critical Care Medicine 2010 181:1**  
**Meeting Abstracts**

Introduction: Guidelines recommend the addition of a LABA to ICS in patients with persistent asthma not controlled on ICS. However, there are few long-term studies supporting this recommendation. Methods: Subjects ( $\geq 12$  yrs) with asthma taking low-medium dose ICS (alone or with LABA or other controllers) were eligible. After a 14-21 day open-label

FP100mcg BID run-in, symptomatic subjects (symptom score of 31, and albuterol use, on 32 days of the 7 immediately prior to randomization) were randomized to FSC 250/50mcg or FP 250mcg BID for 52 weeks. The primary endpoint was the change from baseline in AM pre-dose FEV1. Secondary endpoints included the change from baseline in AM PEF, percentage of symptom-free days, and the rate of asthma attacks (see footnote in Table). Results: 621 subjects from 5 countries were enrolled (mean age=38.1 yrs; mean percent predicted at baseline FEV1=73.5%). Compared with FP alone, there were statistically significant improvements in measures of asthma control (FEV1, AM PEF, symptom and rescue-free days) and there was a non-significant reduction in rate of asthma attacks (per subject per year; p=0.212). The exacerbation rate (per subject per year) was 0.623 (95% CI: 0.423, 0.918; p=0.017), representing a 37.7% reduction in exacerbation rate in favor of FSC. There were no asthma-related deaths in either treatment group. (Table presented) Conclusions: Statistically significant improvements in lung function and patient reported outcomes were achieved over the 52-week treatment period with FSC 250/50 compared with FP 250 alone. The rate of asthma attacks trended towards a reduction and there was a nominally statistically significant reduction in the rate of asthma exacerbations. The effect size of the results may have been mitigated by the unexpected number of subjects with modest symptoms at baseline and improvements in FEV1 during the run-in, a period when many subjects received a dose reduction in their reported pre-study therapy. Both treatments were well tolerated with no meaningful differences between adverse event profiles. In this long-term study evaluating asthma control, FSC was more effective at achieving and maintaining asthma control in symptomatic subjects compared with FP alone.

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