Pharmacy E-News

May 2019

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In this issue:

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New Preferred Inhaled Corticosteroid: Alvesco® (ciclesonide)

By Charlene Liu, PharmD; Reviewed by Bryan Davis, PharmD

Key points:

- Beclomethasone (QVAR®) HFA has been discontinued by the manufacturer and replaced with QVAR® Redihaler which is significantly more expensive. Ciclesonide (Alvesco®) is now Kaiser Permanente Washington's (KPWA) preferred inhaled corticosteroid.
- Studies demonstrate that ciclesonide is similar in safety and efficacy to beclomethasone and has shown efficacy in children aged 5-11 years.
- Pharmacy started converting appropriate patients to the preferred product in February 2019.

Background

- The FDA announced the discontinuation of beclomethasone HFA (QVAR®) metered-dose inhaler (MDI). In November 2018, ciclesonide became KPWA's preferred inhaled corticosteroid (ICS).
- KPWA's Pharmacy and Therapeutics Committee declared ciclesonide (Alvesco®) as therapeutically interchangeable with QVAR® HFA and the QVAR® RediHaler. This decision was endorsed by both Allergy and Pulmonary specialist teams.

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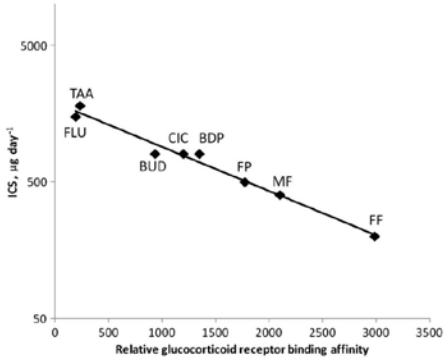
Ciclesonide compared to Beclomethasone

- Data demonstrates that beclomethasone (BDP) and ciclesonide (CIC) have similar efficacy and safety profiles.[1,2]
- CIC and BDP are similar in potency (**Figure 1**) in terms of the relative glucocorticoid receptor binding affinity.
- A Cochrane review found that candidiasis occurred less frequently with CIC compared to other inhaled steroid products. Overall, adverse events were similar in frequency between CIC and BDP.[2]
- The safety profile of CIC is similar to BDP; however, CIC is expected to have interactions with strong inhibitors of cytochrome P450 3A4, such as ketoconazole, cobicistat, and ritonavir.

Figure 1. Relationship between glucocorticoid receptor binding affinity and mid-range nominal therapeutic daily doses of ICS[1]



FLU = flunisolide, TAA = triamcinolone, BUD = budesonide, CIC = ciclesonide, BDP = beclomethasone FP = fluticasone propionate, MF = mometasone, FF = fluticasone furoate

- Ciclesonide is available in two dosage formulations – 80 mcg/actuation and 160 mcg/actuation (**Figure 2**).
- Dosing instructions may differ when a patient is converted from beclomethasone to ciclesonide (**Table 1**).

Figure 2. Image of Alvesco 80 mcg (brown) and Alvesco 160 mcg (orange)

Table 1. Comparison of beclomethasone and ciclesonide

	Beclomethasone[11] (Discontinued)	Ciclesonide[4] (New preferred)
Inhalations per canister	120 inhalations/canister	60 inhalations/canister
Dosing Strengths	40 mcg/actuation 80 mcg/actuation	80 mcg/actuation 160 mcg/actuation
Dosing Instructions	40 mcg: 1-2 puffs twice daily →	80 mcg: 1 puff twice daily
	80 mcg: 1 puff twice daily →	
	80 mcg: 2 puffs twice daily →	160 mcg: 1 puff twice daily
Drug Interactions	None	Potent inhibitors of cytochrome P450 3A4

Evidence Review of Ciclesonide

FDA Approval

- The Food and Drug Administration (FDA) approval of twice daily dosing in patients ≥12 years was based on four studies that showed consistent efficacy with all levels of asthma severity (mild, moderate, and severe). At the time of review, the FDA felt that studies with once daily dosing of CIC failed to show consistent efficacy as seen in pediatric studies in patients aged 4-11 and approved CIC for patients 12 years and older.[3,4]

Evidence for Pediatric Use

- More recent studies demonstrate the efficacy of CIC in children aged 6-11 (**Table 2**).[5-7] The Global Strategy for Asthma Management and Prevention (GINA) guidelines and National Asthma Education and Prevention Program (NAEPP) Asthma Care Quick Reference now recommend CIC in pediatric patients. CIC is approved for use in children aged 6-11 years in Canada, Japan and Australia.[8,9]
- A Cochrane meta-analysis evaluated children aged 4-17 years with chronic asthma. The data showed that there were no significant differences in efficacy between CIC and fluticasone propionate (FP) or budesonide (BUD) based on evaluations of asthma symptoms and exacerbations.[10]
- A randomized, double-blinded, parallel-group study in children with chronic asthma found that CIC had a similar clinical efficacy (i.e., increased forced expired volume [FEV_1] in one second and morning peak expiratory flow [PEF] rates from baseline) compared to FP without suppression of cortisol excretion.[5]

  - Sub-analysis found that CIC 160 mcg was non-inferior to FP 176 mcg for FEV_1, but CIC 80 mcg did not equivalent in efficacy compared to FP 176 mcg.
- Two randomized, double-blinded studies comparing once-daily CIC to placebo in pediatric patients found significant increases from mean morning PEF from baseline were found with all doses of CIC but not with placebo.[6,7]
- Safety profiles (e.g., severe wheeze exacerbations, wheeze-controlled days, growth rates, urinary cortisol levels) were similar between CIC versus placebo across studies.[5-7,10]
- CIC and FP are both options for pediatric patients but CIC is more affordable in cost.

Table 2. Summary of CIC trials in patients <12 years of age

Study	Age	Groups	Efficacy	Safety	Conclusion
Kramer 2013 Meta-analysis[10]	4-17 years	CIC and FP or BUD	• No significant difference in asthma exacerbation events	• Decrease in cortisol levels with BUD compared to CIC • No significant difference in adverse effects with CIC and FP	There are similar improvements in asthma symptoms in patients aged 4-17 years who receive CIC or BUD/FP.
Pedersen 2009 RCT[5]	6-11 years	CIC compared to FP	• CIC was not inferior to FP for FEV_1 • Quality of life improved with all treatments	• Adverse events were comparable	Once-daily CIC is similar in efficacy to FP in patients aged 6-11 years.
Pedersen 2010 RCT[6]	6-11 years	CIC 40, 80, 160 mcg or placebo once daily	• PEF significantly improved with CIC • CIC was superior to placebo for FEV_1 and quality of life	• Adverse events were comparable	Once-daily CIC is effective in children with asthma.
Brand 2011 RCT[7]	2-6 years	CIC 40 mcg, 80 mcg, 160 mcg or	• Low number of wheeze exacerbations requiring systemic	• No differences in safety parameters	CIC modestly reduces exacerbation rates and

		placebo once daily	corticosteroids with CIC • Larger improvements in FVC and FEV_1 compared to placebo		improves lung function.

RCT = Randomized controlled trial, CIC = ciclesonide, FP = fluticasone propionate BUD = budesonide, FEV_1 = forced expired volume, FVC = forced vital capacity

Conclusion

- Ciclesonide is similar in efficacy and safety compared to beclomethasone.
- Although the FDA approved ciclesonide in patients ≥12 years, the efficacy and safety of ciclesonide in children ages 5-11 has been shown to be comparable in terms of safety & efficacy to other ICS in recent analyses.

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Impact of Boosted Anti-Retroviral Therapies on the Pharmacokinetics and Efficacy of Antiplatelet Agents

By Charlene Liu, PharmD; Reviewed by Jeanne Lester, PharmD, BCPS

Key points:

- Ritonavir and cobicistat are potent CYP3A4 inhibitors that may affect the metabolism of clopidogrel and prasugrel, resulting in lower concentrations of their active metabolites.
- Complete platelet inhibition was demonstrated with prasugrel, making prasugrel the preferred therapy among antiplatelets in patients on boosted anti-retroviral therapies.

Background

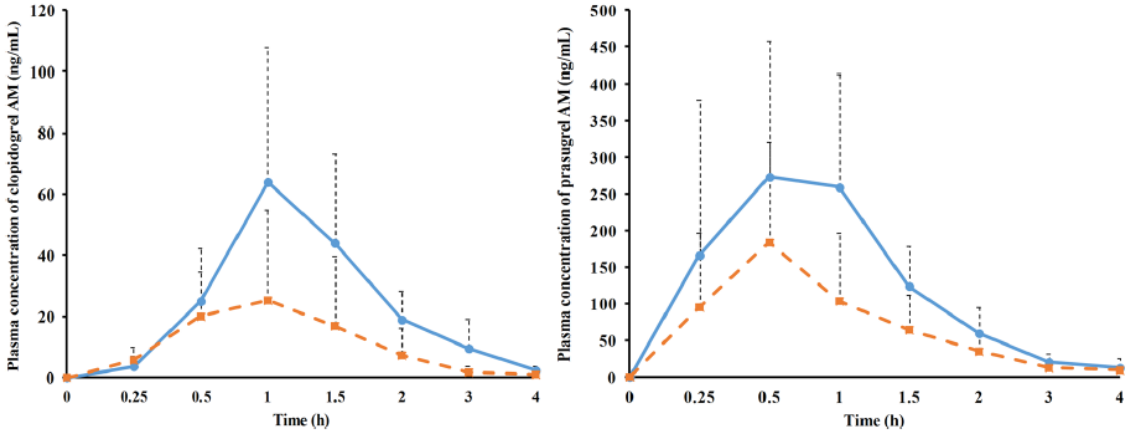
- Ritonavir is a protease inhibitor used in antiretroviral therapies (ARTs) for the treatment of human immunodeficiency virus (HIV). Cobicistat is a pharmacokinetic enhancer often used in ARTs as well. They are potent cytochrome P450 (CYP) 3A4 inhibitors often prescribed to boost the bioavailability of ARTs.
- Patients with HIV with cardiovascular complications are often taking antiplatelet agents with ARTs. Clopidogrel and prasugrel are antiplatelet agents bioactivated to their active metabolites through the CYP3A enzyme. A CYP3A4 inhibitor can potentially prevent the activation of these therapies that require the CYP3A4 enzyme.

- Several studies have evaluated the risk of cardiovascular events in patients with HIV on antiplatelet agents.

Interaction between Boosted ARTs and Antiplatelet Agents

- A case study in Georgia presented a patient with a medication regimen that included isoniazid, clopidogrel, and ritonavir. CYP2C19 and CYP3A4 are required for clopidogrel activation. Given isoniazid is a CYP2C19 inhibitor and ritonavir is a CYP3A4 inhibitor, the patient experienced clopidogrel non-responsiveness due to impaired activation.[12]
- A cross-sectional EVERE$_2$ST-HIV study in France evaluated clopidogrel, prasugrel, ticagrelor, and aspirin's platelet reactivity in patients with HIV. All patients with HIV were on ART, most commonly with ritonavir-boosted protease inhibitors. The study showed a lower efficacy of platelet inhibition with clopidogrel compared to prasugrel in patients with acute coronary syndrome (ACS) and HIV on chronic dual antiplatelet therapy.[13]
    - Most patients were taking clopidogrel (68%) or prasugrel (31%). Only 1% of patients were taking ticagrelor.
- An open label study in Geneva analyzed the interaction between ritonavir and prasugrel in healthy volunteers. The data revealed a significant decrease in the Area Under the Curve (AUC) and maximum concentration (Cmax) of prasugrel when administered with ritonavir compared to prasugrel alone. However, ritonavir did not affect the time to reach maximum concentration and the half-life of prasugrel active metabolite (AM).[14]
    - A limitation to the study is that the ritonavir was administered as a single dose. Therefore, the effects of long-term administration of ritonavir with prasugrel is unknown.
- An open label study in Geneva assessed the impact of ritonavir-boosted ARTs on the efficacy of clopidogrel and prasugrel AMs. Co-administration of ritonavir with an antiplatelet agent demonstrated a 3x lower AUC and Cmax of clopidogrel AM and 2x lower AUC and Cmax of prasugrel AM in patients with HIV concurrently on ARTs compared to healthy volunteers not on ARTs (**Figure 3**).[15]
    - Healthy patients had a 90% higher platelet inhibition compared to patients with HIV after clopidogrel administration. However, almost complete platelet inhibition was seen in all subjects after prasugrel intake despite the reduced exposure of prasugrel AM in patients on ARTs.
    - A limitation to the study is that patients only received a single loading dose of the antiplatelet agents. Therefore, long-term effects of antiplatelet agents when co-administered with ritonavir is unknown.

Figure 3. Mean concentration-time profiles of clopidogrel (left) and prasugrel (right) following single loading doses of clopidogrel and prasugrel in healthy volunteers (solid lines) and patients with HIV (dashed lines).[15]



- There is limited data on concomitant use of ritonavir and ticagrelor.
- Although there is limited evidence, cobicistat is expected to decrease the concentration of antiplatelet agents' active metabolites given it is a potent inhibitor of CYP3A4.

Recommendation

- For patients with HIV on ritonavir or cobicistat therapy, prasugrel (loading dose: 60 mg, maintenance dose: 10 mg) is preferred to clopidogrel as an antiplatelet agent. Patients with a higher risk of bleeding may benefit from a reduced dose of prasugrel (maintenance dose: 5 mg).
- If patients prefer to remain on clopidogrel therapy, providers can consider switching ART to a regimen that do not contain boosting agents.

Conclusion

- Co-administration of ritonavir and antiplatelet agents in patients with HIV result in reduced concentrations of the antiplatelet agent, particularly clopidogrel. A similar effect is expected in patients on cobicistat regimens as well.
- Prasugrel is the preferred antiplatelet therapy in patients who remain on their HIV therapy with boosted agents due to studies demonstrating adequate response despite the interaction.

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Kaiser Permanente Washington Medication Adherence Services Overview

By Janet Kim, PharmD, BCPS

Key Points:

- Kaiser Permanente Washington (KPWA) pharmacy has several tools and programs in place to help their patients stay adherent to chronic medications for diabetes, hypertension, hyperlipidemia, and asthma.
- Patients who fill prescriptions at KPWA pharmacies can benefit from these services.

Background

Supporting patients to stay adherent to their chronic medications is important to achieving their health goals and good clinical outcomes. Quality metrics on adherence to hypertension (HTN), diabetes, and hyperlipidemia (i.e., statins) medications are monitored and highly weighted in the Centers of Medicare and Medicaid Services (CMS) Star Ratings. Adherence to other drug classes such as asthma controller medications, antidepressants, antiretrovirals, and anticoagulants are also monitored and/or reported by other quality rating organizations (e.g., NCQA/HEDIS) or within Kaiser Permanente regions.

Kaiser Permanente Washington (KPWA) has several pharmacy and clinic tools and programs in place to help patients stay adherent to these chronic medications, with heavier support on select drug classes for HTN, diabetes, or hyperlipidemia (**Table 3**). Although supporting adherence to any chronic medication is important, KPWA is prioritizing (or starting with) these three drug classes because they provide strong evidence (e.g., mortality benefit) in the nation's top disease states in terms of patient volume and deaths, and overall healthcare costs.[16] KPWA data shows that overall more patients are consistently adherent to their medications when they fill prescriptions at KPWA pharmacies, including mail order, compared to those who fill outside at non-KPWA pharmacies.

Live-Outreach Pharmacy Program

KPWA has a live outreach pharmacy adherence program that supports Medicare members in filling their diabetes, statins, and angiotensin-converting enzyme inhibitors (ACE/ARBs) on time at KPWA pharmacies or mail order. KPWA Medicare members who do not fill at KPWA pharmacies or mail order are not included in this program at this time. Providers are encouraged to recommend their Medicare patients to fill at KPWA pharmacies so that they can receive this service. Please note that this program is only initiating outbound calls for diabetes, statins,

ACE/ARBs refills at this time; however, staff do help patients fill their other prescriptions while on the call. If adherence barriers are identified during call, pharmacists will document in the encounter the barriers and suggested recommendations discussed with patients.

Other outreach programs also exist to support adherence to direct-acting oral anticoagulants (DOACs) by KPWA Anticoagulant Management Services and specialty medications (Hepatitis C, oral oncology, etc.) by KPWA Specialty Pharmacy for the patients they service.

IVR Robo Refill Reminder calls

Interactive voice response (IVR) robo refill reminder calls are made to KPWA Medicare members (whether filling with KPWA pharmacy or non-KPWA pharmacy) for their diabetes, statins, ACE/ARBs, and asthma controller medications. IVR calls are also made to KPWA commercial members for their asthma controller medications. Members will receive a call 5 days before their next refill due date and again 2 days after their expected refill due date if overdue.

Opportunistic Pharmacist Consult in Clinic

KPWA frontline pharmacy staff receive alerts when filling any medication for a patient who may be non-adherent to their diabetes, statins, or ACE/ARB medications based on their prescription fill history in the past 12 months. These alerts prompt staff to ask patients if they'd like to pick up (or have mailed) these other medications as well. Pharmacists also provide a quick adherence consult to patients at the window.

Table 3. KPWA pharmacy strategies to support medication adherence

Pharmacy Services	Member Criteria	Drug classes
Several days prior to refill due date and/or if overdue		
Live outreach	Medicare KPWA pharmacy and mail order only	non-insulin diabetes, statins, ACE/ARBs
	Medicare and commercial Anticoagulant management service enrolled patients	Direct-acting oral anticoagulants
	Medicare and commercial KPWA Specialty Pharmacy only	Hepatitis C, oral oncology, & other select specialty drugs
IVR robo call	Medicare* KPWA and non-KPWA pharmacies	non-insulin diabetes, statins, ACE/ARBs, asthma controllers
Opportunistic RPH consult in clinic	Medicare and commercial KPWA pharmacy only	non-insulin diabetes, statins, ACE/ARBs

Pick up reminders for ready meds		
Robo call and secure message	Medicare and commercial KPWA pharmacy only	All medications
Text messaging		All medications
Last call before return Rx to shelf		non-insulin diabetes, statins, ACE/ARBs

ACE/ARB=angiotensin converting enzyme inhibitors/ angiotensin receptor antagonists;
IVR=interactive voice response
*Commercial included for asthma controllers only

Conclusion

KPWA helps support their patients to stay adherent to chronic medications via live-outreach calls, robo calls, opportunistic front counter pharmacist consults, secure messaging, and text messaging. Although these interventions are currently targeted to select chronic medications, discussions are underway in expanding refill reminder tools to additional drug classes.

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Safety Alert: Budesonide Respules (Pulmicort®)

By Bryan Davis, PharmD

Background

- It has come to pharmacy's attention that Pulmicort Respules are frequently ordered for infant nebulization without assuring that patients/caregivers use it only with a jet nebulizer and with a Pari face mask (**Figure 4**). This presents not only a problem of medication efficacy but also patient safety.
- The directions for use from the package insert specify that Respules should be administered via a jet nebulizer (ultrasonic nebulizers are not suitable for adequate administration and are NOT recommended). A Pari Mask is necessary to reduce the eye exposure to steroids to reduce the risk of glaucoma and cataracts. The typical aerosol face mask has large eye vents on the top of the mask and is a bottom loaded design which directs the aerosol upward toward the eyes.

Figure 4. Pediatric Jet Nebulizer with Pari Face Mask

Recommendation

- If providers plan to use Pulmicort Respules for pediatric use, specify “Pari nebulizer and Pari mask” when the order is placed.

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FDA Medication Alert

Drug	Safety Alert	Link
Xeljanz®, Xeljanz XR® (tofacitinib)	**Increased Risk of Blood Clots in the Lungs and Death with Higher Dose in Rheumatoid Arthritis Patients** Increased risk of blood clots in the lungs and death was found when the tofacitinib 10 mg twice daily dose was used in patients with rheumatoid arthritis (RA). This dose for RA was not FDA approved. There is currently one KPWA patient with a rheumatology prescriber filling this dose. Providers should follow the recommendation in the prescribing information and monitor patients for signs and symptoms of pulmonary embolism.	Link

Uloric (febuxostat)	**Boxed Warning Added due to Increased Risk of Death** Increased risks of cardiovascular-related and all-cause death have been seen with febuxostat. The FDA recommends reserving febuxostat only for patients with gout who have failed or are intolerant to allopurinol. Providers should trial patients on allopurinol first for gout and counsel patients who need to take febuxostat on its cardiovascular risks.	Link

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