Pharmacokinetics of Dolutegravir After Switching to Abacavir/Dolutegravir/ Lamivudine From an Efavirenz-Based Regimen: A PK Sub-Study From STRIIVING

Joss de Wet,[1] Edwin DeJesus,[2] Louis Sloan,[3] Justin Koteff,[4] Clare Brennan,[4] Kimberly Adkison,[4] Deanna Merrill,[5] Brian Wynne,[6] Mark Shaefer,[4] Michael Aboud [7]

[1]University of British Columbia, Vancouver, BC, Canada; [2]Orlando Immunology Center, Orlando, FL, USA; [3]North Texas Infectious Diseases Consultants, Dallas, TX, USA; [4]ViiV Healthcare, Research Triangle Park, NC, USA; [5]ViiV Healthcare, Castle Rock, Colorado, USA; [6]ViiV Healthcare, Collegeville, PA, USA; [7]ViiV Healthcare, London, UK

UK/DTGP/0037/16k
Prepared March 2017

Prescribing information can be found at the end of the presentation

17th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy; June 8-10, 2016; Washington, DC

Introduction

- Triumeq® (ABC/DTG/3TC) is the first single-tablet regimen that contains DTG and is tenofovir (TDF)–free
- Triumeq was approved in North America in August 2014 and in Europe in September 2014
- The STRIIVING study (NCT02105987) was conducted to evaluate the efficacy, safety, tolerability, and treatment satisfaction of switching to Triumeq in subjects stable and suppressed on a variety of regimens
- The study enrolled April 2014 to October 2014

de Wet et al. Clin Pharm 2016; Washington, DC. Abstract O_23.

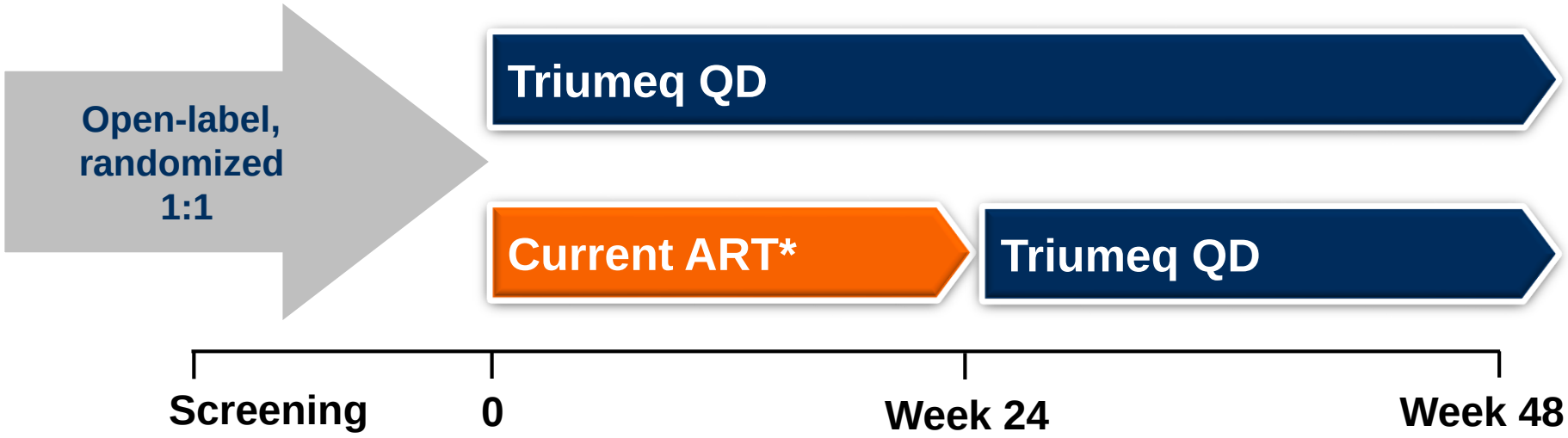
Introduction

- DTG is metabolized primarily by UGT1A1 and is a minor substrate for CYP3A4
- Co-administration of DTG 50 mg once daily with efavirenz (EFV), a CYP3A4 and UGT1A1 inducer, 600 mg once daily decreased DTG AUC and $C\tau$ by 57% and 75%, respectively,[1] necessitating BID dosing of DTG upon co-administration of EFV
- Generaux et al, in a SimCYP simulation, predicted there would be no time when both drugs would fall below target concentrations[2] and justified conducting the study post-EFV
- This sub-study of the STRIIVING study evaluated the duration of EFV induction effect on the PK properties of DTG when virologically suppressed patients were switched from an EFV-based regimen to a DTG-based regimen

1. Song et al. *Eur J Clin Pharmacol.* 2014;70:1173-1179. **2.** Generaux et al. Clin Pharm 2014; Washington, DC. Poster P_36.
de Wet et al. Clin Pharm 2016; Washington, DC. Abstract O_23.

STRIIVING Study Design

Countries: US, Canada, Puerto Rico



Inclusion criteria

- Virologically suppressed (confirmed HIV-1 RNA <50 c/mL)
- HLA-B*5701 negative

Primary endpoint at 24 weeks: VL <50 c/mL (Snapshot)

Assessments

- CD4 cell count changes
- Clinical and laboratory safety
- Lipids, renal, bone, and cardiovascular changes
- Development of resistance
- Treatment satisfaction

*Stable suppressive current ART with 2 NRTIs plus either a PI, an NNRTI, or an INI. ≥40% PIs, at least 25% INIs.

90% power based on 10% non-inferiority margin (estimated response rate = 85%).

de Wet et al. Clin Pharm 2016; Washington, DC. Abstract O_23.

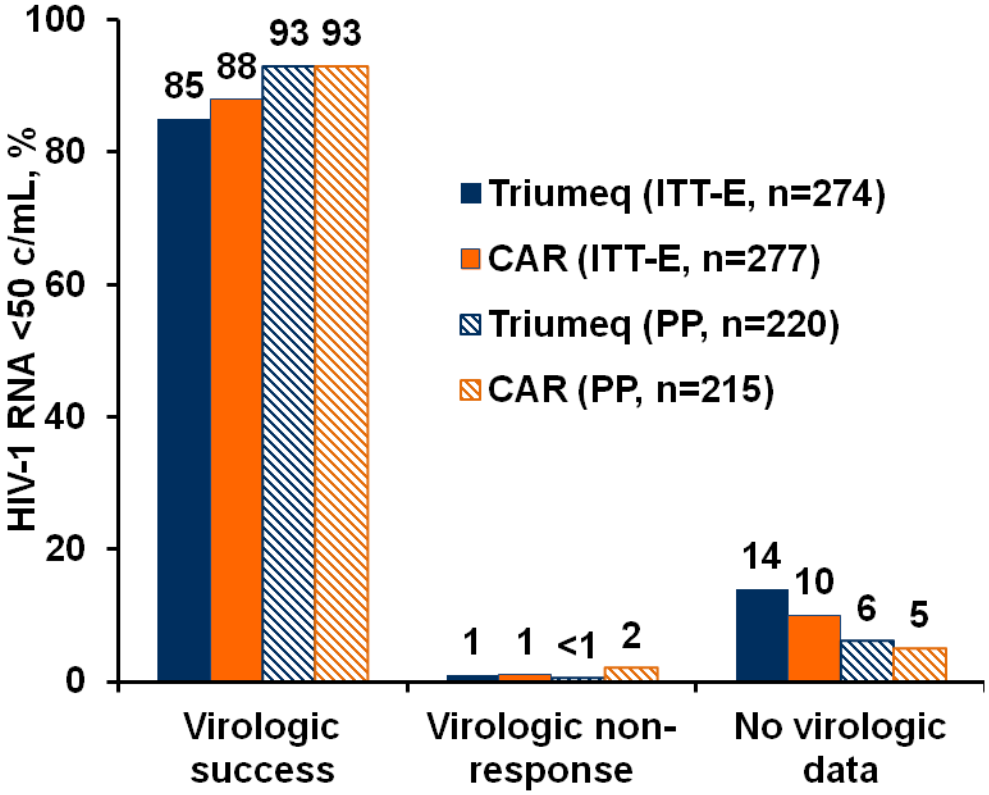
PK Sub-Study Design

- 24 patients on an EFV-based regimen were enrolled in the PK sub-study
  - Early switchers (ES) were subjects randomized to switch to Triumeq and start treatment on Day 1
  - Late switchers (LS) were subjects randomized to continue their current regimen until Week 24 when they switched to Triumeq
- Blood samples for evaluation of DTG and EFV plasma PK were collected prior to the DTG dose on Day 1 and at Weeks 1, 2, 4, 8, and 24 (ES) and Weeks 24, 25, 26, 28, 32, and 48 (LS)
- DTG and EFV plasma concentrations were measured by validated LC/MS/MS methods with LOQ of 20 and 0.1 ng/mL, respectively

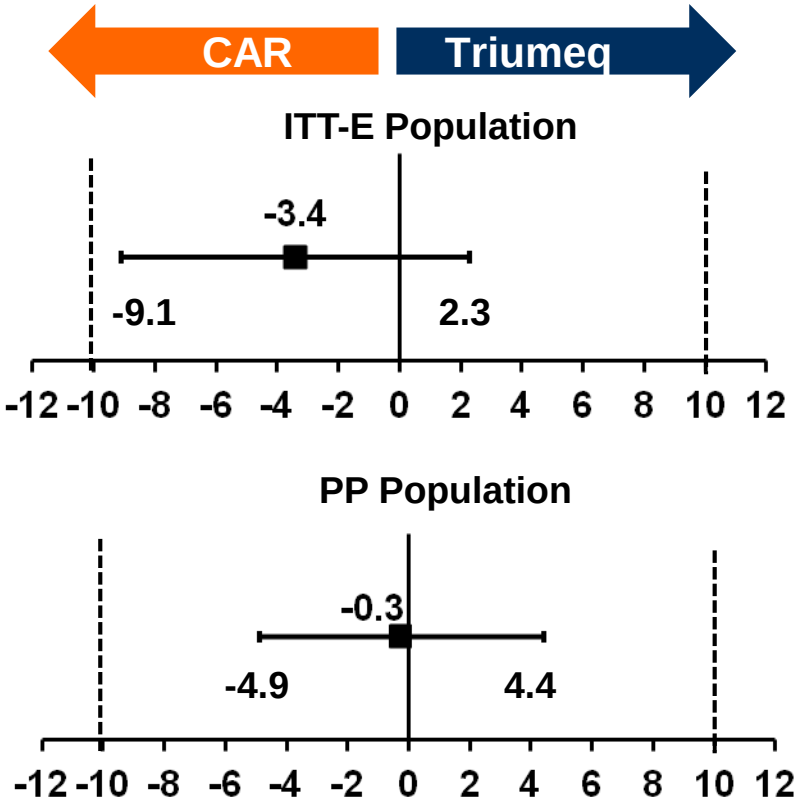
de Wet et al. Clin Pharm 2016; Washington, DC. Abstract O_23.

Overall Snapshot Outcomes at Week 24: ITT-E and PP Populations

Virologic outcomes



Treatment differences (95% CI)



CI, confidence interval; ITT-E, intent-to-treat exposed; PP, per protocol.

- Virologic suppression was maintained through Week 48 in the ES arm. The proportion of LS subjects with HIV-1 RNA <50 c/mL at Week 48 was comparable to the proportion at Week 24 for the ES arm*

*Full 48-week results to be presented at a conference later this year.

Trottier et al. ICAAC 2015; San Diego, CA.

de Wet et al. Clin Pharm 2016; Washington, DC. Abstract O_23.

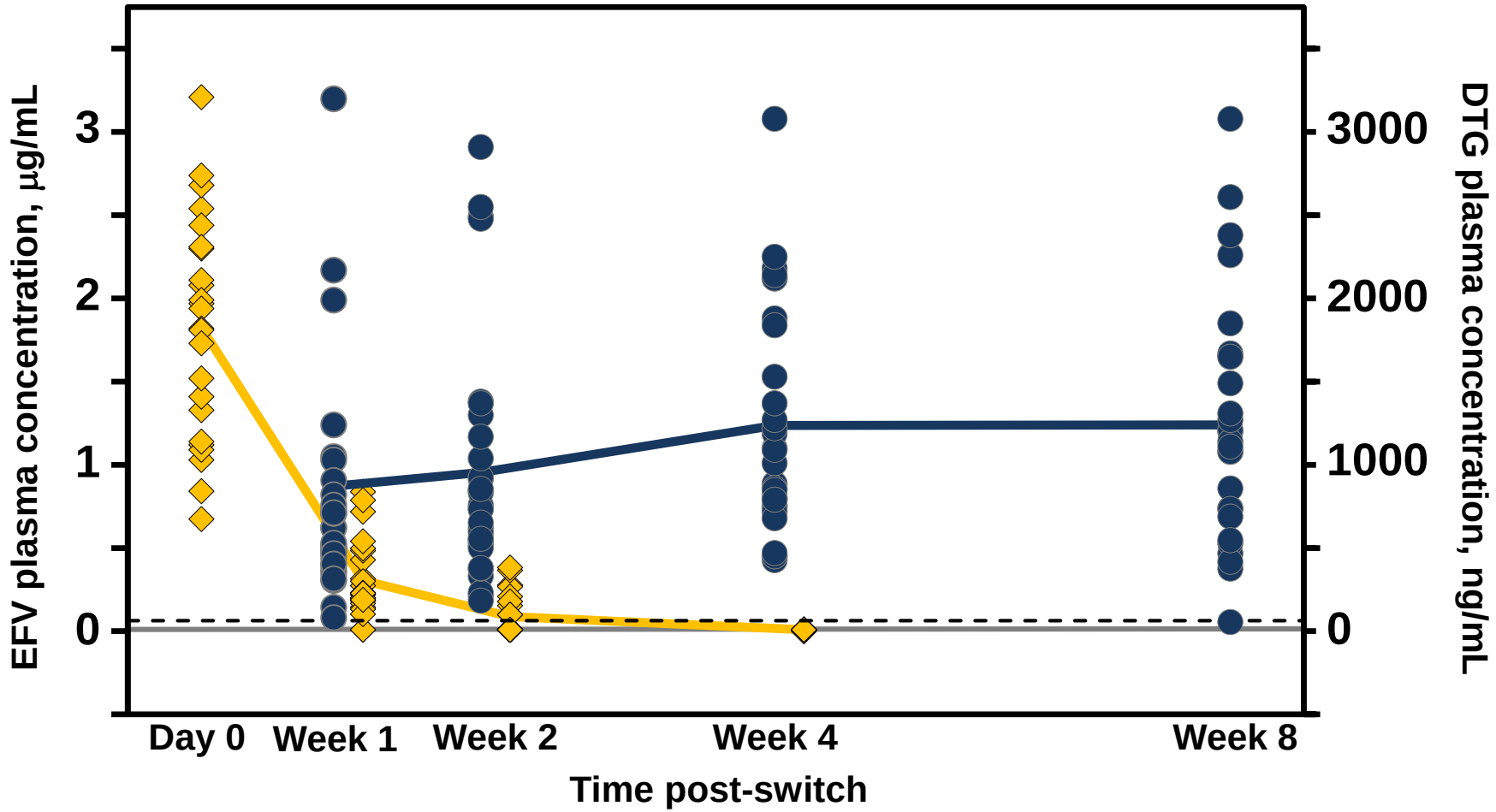
PK Results

Time since switch	Visit, early switcher/ late switcher	Pre-dose DTG, ng/mL mean (SD)	Residual EFV, μg/mL mean (SD)
Day 0	Day 1/Week 24	– (n=0)	1.83 (0.66) (n=24)
Week 1	Week 1/Week 25	938.20 (955.21) (n=24)	0.32 (0.23) (n=21)
Week 2	Week 2/Week 26	860.52 (627.49) (n=27)	0.14 (0.09) (n=23)
Week 4	Week 4/Week 28	1219.33 (709.65) (n=24)	0.090 (0.00) (n=20)
Week 8	Week 8/Week 32	1186.17 (713.95) (n=15)	– (n=0)
Week 24	Week 24/Week 48	1378.23 (1017.98) (n=23)	– (n=0)

DTG, dolutegravir; EFV, efavirenz; PK, pharmacokinetic; SD, standard deviation.

de Wet et al. Clin Pharm 2016; Washington, DC. Abstract O_23.

Pre-dose DTG and Residual EFV Plasma Concentration-Time Plot



de Wet et al. Clin Pharm 2016; Washington, DC. Abstract O_23.

Maintenance of Viral Suppression

	HIV-1 RNA by subject, copies/mL																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Day 1	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50
Week 1	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50
Week 2	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50
Week 4	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50
Week 8	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50
Week 24	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50

17th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy; June 8-10, 2016; Washington, DC

Conclusions

- After switching to Triumeq, residual EFV plasma concentrations steadily decreased and DTG Cmin steadily increased reaching steady-state by 4 weeks post switch
- DTG mean concentrations were maintained above PA IC90 at all sample times and there was no time in the immediate post-switch period at which both EFV or DTG measured concentrations fell below their respective IC90 concentrations
- These PK data, along with the maintained virologic suppression, support switch to Triumeq from an EFV-containing regimen without need for DTG dosage adjustment

de Wet et al. Clin Pharm 2016; Washington, DC. Abstract O_23.

Acknowledgments

- This study was funded by ViiV Healthcare
- We thank everyone who has contributed to the success of this study, including
  - All study participants and their families
  - The GSK and ViiV Healthcare study teams
  - PPD
  - The clinical investigators and their staffs

Canada

Baril, Conway, de Wet, Fraser, Kasper, LeBlanc, Logue, Loutfy, Rachlis, Trottier, Walmsley

Puerto Rico

Marquez, Melendez- Rivera, Santiago Colon, Zorrilla

United States

Baxter, Benson, Bhatti, Blick, Bolan, Bredeek, Brennan, Brinson, Calvo, Chang/P. Johnson, Cunningham, Cutro, DeJesus, Dietz, Dretler, Dube, Edelstein, Evans/Martin, Feinberg, Felizarta, Fife, Flamm, Gallant, Garcia-Diaz, Grossberg, Hagins, Hare, Henry, Hite, Hoffman-Terry, Hsiao, Huhn, Jain, Jayaweera, L. Johnson, M. Johnson, Kinder, Klein, Kumar, Lake, Lalezari, Lewis, Martorell, McDonald, Meier, Mills, Mounzer, Nahass, Newman, Nguyen, Novak, Osiyemi, Parks, Pierone, Prelutsky, Ramgopal, Rashbaum, Rhame, Richmond, Riddell, Ruane, Salazar/ Rodriguez Scarsella, Schneider, Schrader, Scott, Scribner, Sha, Shalit, Shamblaw, Shikuma, Shon, Simon, Sloan, Small/Khoury, Stefanic, Van Dam, Vanig, Wade, Ward, Wheeler

Prescribing Information
Triumeq® ▼ dolutegravir 50mg/abacavir 600mg/lamivudine 300mg tablets
See Summary of Product Characteristics before prescribing.
Indication: HIV in over 12 years and ≥ *40kg*. Screen for HLA-B*5701 prior to use. Do not use if HLA-B*5701 positive. **Dose:** one tablet once daily with or without food. *Elderly:* Limited data in 65+ yrs. *Creatinine clearance <50ml/min* or *moderate/severe hepatic impairment:* Not recommended. Monitor closely in mild hepatic impairment.
Contraindications: Hypersensitivity to any ingredient. Co-administration with dofetilide.
Warnings/precautions: Both abacavir and dolutegravir are associated with risk of hypersensitivity reactions (HSR). Do not initiate in HLA-B*5701+ or previous suspected abacavir HSR. Stop Triumeq without delay if HSR suspected. Never reintroduce any dolutegravir- or abacavir-containing product after suspected HSR. Risks of immune reactivation syndrome, osteonecrosis, increased weight, lipids, glucose. Monitor LFTs in Hepatitis B/C co-infection. Inconclusive data on relationship between abacavir and MI; minimise all modifiable CV risk factors (e.g. smoking, hypertension, hyperlipidaemia). Not recommended if dolutegravir required b.d. (with etravirine [without boosted PI], efavirenz, nevirapine, rifampicin, boosted tipranavir, carbamazepine, oxcarbazepine, phenytoin, phenobarbital and St John's Wort). Use with cladribine not recommended. Use with Mg/Al-containing antacids, calcium, multivitamins or iron requires dosage separation. Caution with metformin: monitor renal function and consider metformin dose adjustment.
Pregnancy/lactation: Not recommended. Avoid breast-feeding. **Side effects:** See SPC for details. Headache, insomnia, sleep/dream disorders, GI disturbance, fatigue, hypersensitivity, anorexia, depression, dizziness, somnolence, lethargy, malaise, cough, nasal symptoms, rash, pruritus, alopecia, arthralgia, myalgia, asthenia, fever, elevations of ALT, AST and CPK, blood dyscrasias, suicidal ideation or suicide attempt, rhabdomyolysis, lactic acidosis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis. **Basic NHS costs:** 30 tablets: £798.16
EU/1/14/940/001. MA holder: ViiV Healthcare UK Ltd, 980 Great West Road, Brentford, Middlesex TW8 9GS. Further information is available from Customer Contact Centre, GlaxoSmithKline UK Ltd, Stockley Park West, Uxbridge, Middlesex UB11 1BT.

POM S1A

Date of approval: January 2017 Zinc code: UK/TRIM/0037/14(7)

Adverse events should be reported. For the UK, reporting forms and information can be found at *www.mhra.gov.uk/yellowcard*. Adverse events should also be reported to GlaxoSmithKline on 0800 221 441.

Adverse events should be reported. For Ireland, adverse events should be reported directly to the HPRA; Freepost, Pharmacovigilance Section, Health Products Regulatory Authority, Earlsfort Terrace, Dublin 2, Tel: +353 1 676 4971, *medsafety@hpra.ie*. Adverse events should also be reported to GlaxoSmithKline on 1800 244 255.