Mira, Mira on the wall; will Mirabegron fix urinary incontinence for all?

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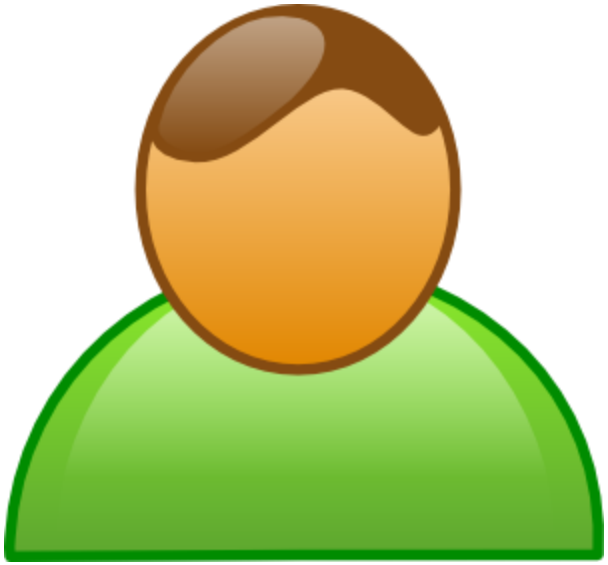
November 28, 2013

Case: JM



- 77 year old male
- 5’7”, 102kg
- Admission for COPD
  - In hospital for 7 days

- Dr ordered “Medication for incontinence – per pharmacy”

Case: JM

PMHx	Obese, COPD, GERD
Current Medications	Advair Diskus Salbutamol Nebs Ipratroprium nebs Pantoprazole
Allergies	No Known
Social Hx	50 pack year smoker
Labs	N/C
Urinary Symptoms	Urinate >10x/day Often doesn't make commode Wakes up 2x/night to urinate ***ONGOING FOR >6 MONTHS***

Overactive Bladder

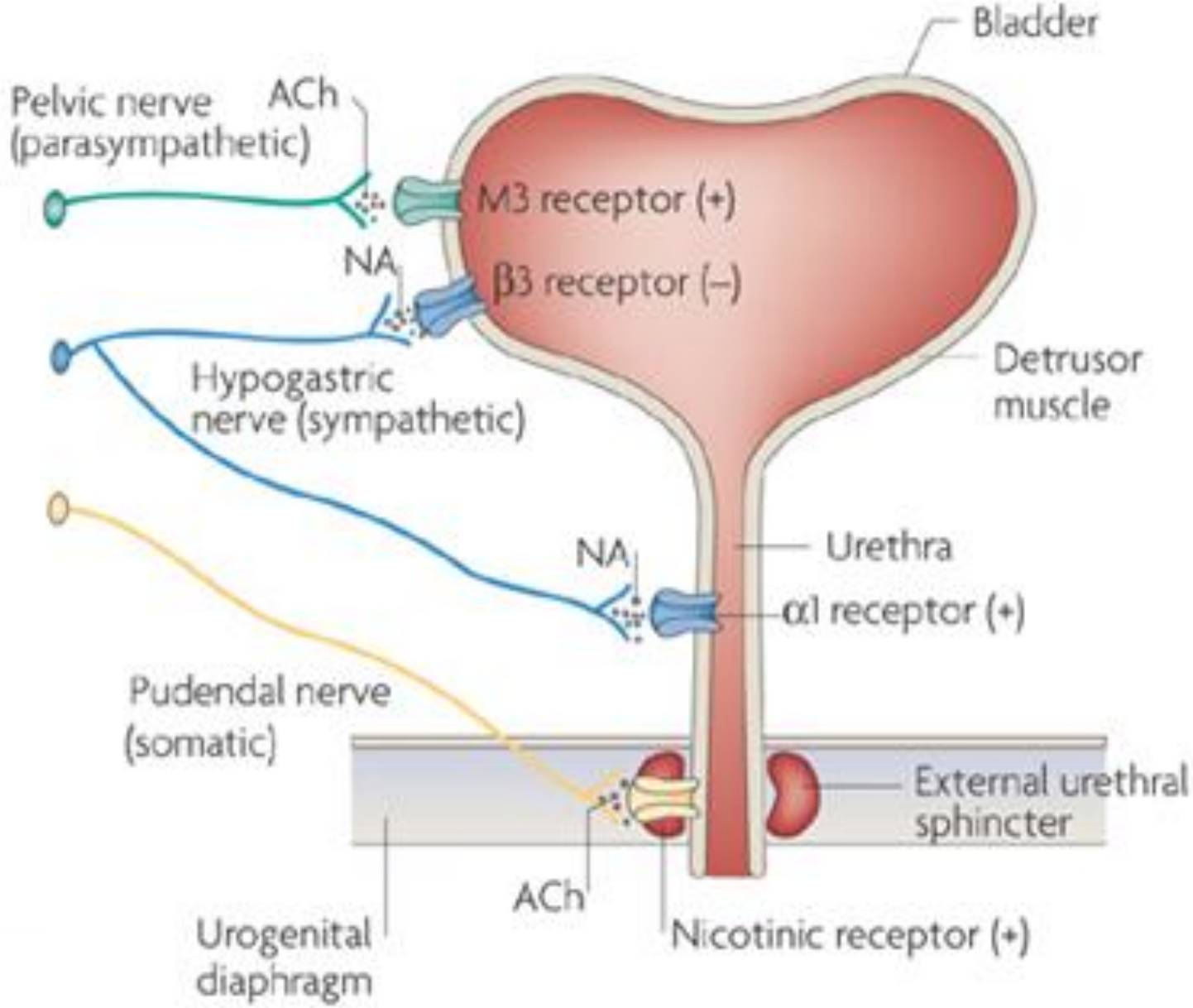
OAB - Importance

- 18% of Canadians have overactive bladder
- Defined in trials:
  - For ≥ 3 months
    - ≥8 micturitions per 24 hrs
      +
    - ≥1 urgency episodes with or without incontinence per 24 hrs
- Complications
  - Skin breakdown
  - UTIs
  - Professional life
  - Personal life

Can J Urol. 2004 Jun;11(3):2278-84.

OAB Treatment Modalities

- Non pharmacologic
- Pharmacologic
  - Oxybutynin
  - Tolterodine
  - ?others
- Surgery



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FDA Advisory Committee Recommends Approval of Mirabegron - Investigational Overactive Bladder Treatment from

Medscape Medical News > Conference News

Mirabegron Showing Promise for Overactive Bladder

Kate Johnson
April 09, 2013

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FDA NEWS RELEASE

For Immediate Release: June 28, 2012
Media Inquiries: Stephanie Yao, 301-796-0394, stephanie.yao@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA approves Myrbetriq for overactive bladder

For Immediate Release

FDA Approves Overactive Bladder Treatment Myrbetriq™ (mirabegron) from Astellas

Myrbetriq is the first and only beta-3 adrenergic agonist indicated for the treatment of overactive bladder

P	In a patient with OAB symptoms	
I	Mirabegron	
C	Standard Therapy or Placebo	
O	*Efficacy*	Mortality Quality of Life # Episodes incontinence/day # Episodes nocturia/night # Episodes of urge/day # Voids/day
	Safety	SAE Withdrawals due to ADR Total ADRs

Database	EMBASE, Pubmed, IPA, Cochrane Library, clinicaltrials.gov
Search Terms	Mirabegron, Overactive Bladder, Urinary Incontenence, YM178
Limits	Human, English
Results	**•1 SR** **•5 RCTs** •4 vs placebo in the SR •1 vs tolterodine •14 PK Papers •22 Reviews

SR	RCT
The efficacy and safety of mirabegron in treating OAB: a SR and MA of phase III trials Int Urol Nephrol. 2013 Jul 30. [Epub ahead of print]	Study to Assess 12-Month Safety and Efficacy of Mirabegron, a β3-Adrenoceptor Agonist, in Overactive Bladder Eur Urol. 2013 Feb;63(2):296-305.

SR - Cui et al.

Question	Does Mirabegron 50mg reduce symptoms of OAB compared to placebo
Search	Medline, Embase, Cochrane Controlled Trials Register database
Inclusion	1. Analyzable data 2. Access to full text
Assessment	Jadad
Patient #	5761
Outcomes	a) Decrease μ micturitions /24 h b) Decrease μ urgency episodes /24 h c) Decrease μ incontinence episodes/24 h

Int Urol Nephrol. 2013 Jul 30. [Epub ahead of print]

SR – Cui et al.

Study	Therapy in experimental group	Therapy in control group	Country	Sample size		Administration method	Duration of treatment	Dosage (weeks)	Inclusion population (mg/day)
				Experimental	Control				
Scorpio	Mirabegron	Placebo	Europe and Australia	497	497	Oral	12	50	Men and women ≥18 years of age with symptoms of OAB for ≥3 months
Aries	Mirabegron	Placebo	US and Canada	442	454	Oral	12	50	Men and women ≥18 years of age with symptoms of OAB for ≥3 months
Capricorn	Mirabegron	Placebo	US, Canada, Europe and Australia	440	433	Oral	12	50	Patients ≥18 years of age with symptoms of OAB for ≥3 months
178-CL-048	Mirabegron	Placebo	Japan	380	381	Oral	12	50	Adult patients with OAB symptoms for ≥24 weeks

OAB overactive bladder

Int Urol Nephrol. 2013 Jul 30. [Epub ahead of print]

SR – Cui et al.

Study	Allocation sequence generation	Allocation concealment	Blinding	Loss to follow-up	Calculation of sample size	Statistical analysis	Level of quality
Scorpio	A	A	A	101	Yes	Analysis of variance	A
Aries	A	A	A	[illegible]	Yes	Analysis of variance	A
Capricorn	A	A	A	[illegible]	Yes	Analysis of variance	A
178-CL-048	A	A	A	62	Yes	Analysis of variance	A

A all quality criteria met (adequate): low risk of bias, *B* one or more of the quality criteria only partly met (unclear): moderate risk of bias, *C* one or more criteria not met (inadequate or not used): high risk of bias

Int Urol Nephrol. 2013 Jul 30. [Epub ahead of print]

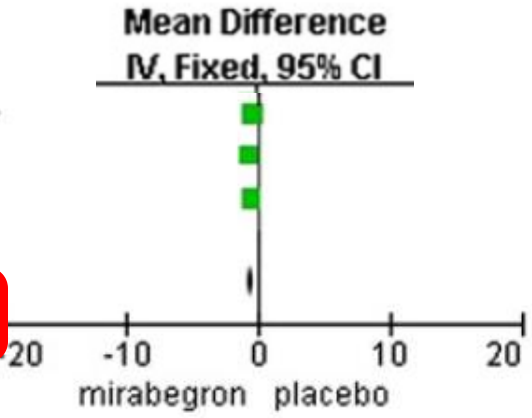
SR – Cui et al.

Decrease in μ # of urgency episodes per 24 h

(d)

Study or Subgroup	mirabegron Mean	SD	Total	placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
178-CL-048	-1.85	2.56	380	-1.37	3.19	381	35.2%	-0.48 [-0.89, -0.07]
ARIES	-1.57	3.29	424	-0.82	3.33	433	30.3%	-0.75 [-1.19, -0.31]
SCORPIO	-2.25	3.25	470	-1.65	3.28	479	34.5%	-0.60 [-1.02, -0.18]
Total (95% CI)			**1274**			**1293**	**100.0%**	**-0.60 [-0.85, -0.36]**

Heterogeneity: Chi² = 0.77, df = 2 (P = 0.68); I² = 0%
Test for overall effect: Z = 4.85 (P < 0.00001)



-0.60 (-0.85,-0.36)

Int Urol Nephrol. 2013 Jul 30. [Epub ahead of print]

SR – Cui et al.

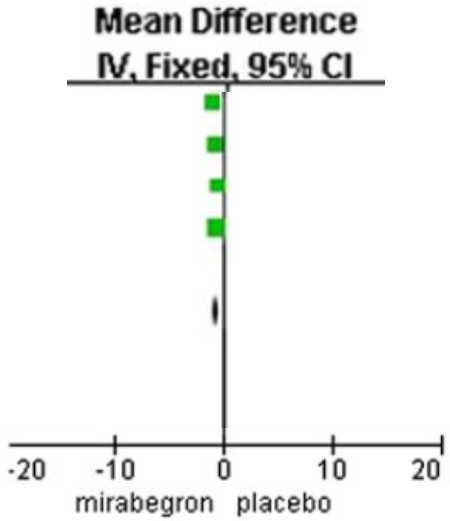
Decrease in μ # of micturitions /24 h

(b)

Study or Subgroup	mirabegron Mean	SD	Total	placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
178-CL-048	-1.67	2.21	380	-0.86	2.35	381	27.9%	-0.81 [-1.13, -0.49]
ARIES	-1.66	2.68	425	-1.05	2.71	433	22.5%	-0.61 [-0.97, -0.25]
CAPRICORN	-1.62	2.68	426	-1.15	2.83	415	21.1%	-0.47 [-0.84, -0.10]
SCORPIO	-1.94	2.52	473	-1.37	2.52	480	28.6%	-0.57 [-0.89, -0.25]
Total (95% CI)			**1704**			**1709**	**100.0%**	**-0.62 [-0.80, -0.45]**

Heterogeneity: $Chi^2 = 2.04$, $df = 3$ ($P = 0.56$); $I^2 = 0\%$

Test for overall effect: $Z = 7.16$ ($P < 0.00001$)



-0.62 (-0.80,-0.45)

Int Urol Nephrol. 2013 Jul 30. [Epub ahead of print]

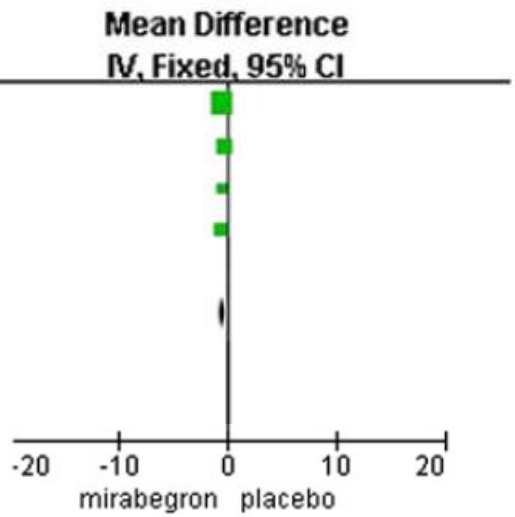
SR – Cui et al.

Decrease in μ # of incontinence episodes/24 h

(a)	mirabegron			placebo				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
178-CL-048	-1.12	1.48	380	-0.66	1.86	381	41.5%	-0.46 [-0.70, -0.22]
ARIES	-1.47	1.94	312	-1.13	1.98	325	25.5%	-0.34 [-0.64, -0.04]
CAPRICORN	-1.38	1.97	257	-0.89	2.57	262	15.3%	-0.49 [-0.88, -0.10]
SCORPIO	-1.62	2.35	293	-1.13	2.15	291	17.7%	-0.49 [-0.86, -0.12]
Total (95% CI)			**1242**			**1259**	**100.0%**	**-0.44 [-0.59, -0.29]**

Heterogeneity: $Chi^2 = 0.58$, $df = 3$ ($P = 0.90$); $I^2 = 0\%$

Test for overall effect: $Z = 5.60$ ($P < 0.00001$)



-0.44 (-0.59,-0.29)

Int Urol Nephrol. 2013 Jul 30. [Epub ahead of print]

SR - Appraisal

Limitations	•Clinical Question •Dose + Placebo comparator •SR Search strategy •Only Medline, Embase, Cochrane •No unpublished or grey literature •Astellas Pharma sponsored •Publication bias •Clinical application •Excellent adherence •Healthier patients

SR	RCT
The efficacy and safety of mirabegron in treating OAB: a SR and MA of phase III trials Int Urol Nephrol. 2013 Jul 30. [Epub ahead of print]	Study to Assess 12-Month Safety and Efficacy of Mirabegron, a β3-Adrenoceptor Agonist, in Overactive Bladder Eur Urol. 2013 Feb;63(2):296-305.

RCT – Chapple et al.

Design	**2wk run in, R, DB, AC, 12 months**
Population	n=2444 ~60 years old, ~95% white, ~75% female 11 micturations/24 hr 2 nocturia episodes/24 hr ***Inclusion***: symptoms of OAB, ≥8 micturations/24hr, ≥3 urge episodes/3 days ***Exclusion***: Obstruction, if stress incontinence was major diagnosis, use of other OAB medications, self catheterization

Eur Urol. 2013 Feb;63(2):296-305.

RCT – Chapple et al.

Intervention	Mirabegron 50mg daily Mirabegron 100mg daily
Comparator	Tolterodine 4mg ER daily
Objective	***Primary*** Incidence/Severity of TEAE ***Secondary*** Change in OAB symptoms

Eur Urol. 2013 Feb;63(2):296-305.

RCT – Chapple et al.

Effect	Mirabegron 50mg (n=812)	Mirabegron 100mg (n=820)	Tolterodine 4mg (n=812)
SAE	5.2%	6.2%	5.4%
TEAE	59.7%	61.3%	62.6%
Withdrawal - ADE	6.4%	5.9%	6.0%
HTN	9.2%	9.8%	9.6%
Dry Mouth	2.8%	2.3%	8.6%

Eur Urol. 2013 Feb;63(2):296-305.

RCT – Chapple et al.

Effect	Mirabegron 50mg (n=812)			Mirabegron 100mg (n=820)			Tolterodine 4mg (n=812)		
	BL	EOT	Δ	BL	EOT	Δ	BL	EOT	Δ
OAB-q	44.6	31.5	-13.1	44.3	29.5	-14.8	44.2	29.9	-14.3
Micturitions / 24hr	11.13	9.83	-1.30	11.16	9.73	-1.43	10.94	9.47	-1.47
Incontinence / 24hr	2.66	1.61	-1.05	2.49	1.26	-1.23	2.42	1.09	-1.33
# Nocturia / 24hr	2.08	1.62	-0.46	2.11	1.72	-0.39	2.02	1.59	-0.43

BL = Baseline, EOT = End of therapy (12 months)

Eur Urol. 2013 Feb;63(2):296-305.

RCT – Chapple et al.

Limitations	•Design •Missing apriori TEAE •No sample size calculation •Unblinding •80% patients already in prior phase 3 trial •Selection bias •Severity of outcomes •"Most TEAE were mild or moderate" •Astellas Pharma sponsored •Clinical application •Excellent adherence •Healthier patients •No comment on cognitive impairment

Eur Urol. 2013 Feb;63(2):296-305.

Whats up in Canada?

Health Canada Santé Canada

Type, Control Number	Submitted	and Date	Summary of Activities
Drug product (DIN 02402874, 02402882) market notification	Not applicable	Date of first sale: 2013/03/28	The manufacturer notified Health Canada of the date of first sale pursuant to C.01.014.3 of the *Food and Drug Regulations*.
NDS # 153806	2012/03/19	Issued NOC 2013/03/06	Notice of Compliance issued for New Drug Submission.

ctivities are listed first)

Canadian Agency for Drugs and Technologies in Health

7	Embargo Period [5] Manufacturers may make a Request for Reconsideration and Drug Plans may make a Request for Clarification of the Recommendation	10	2013-Aug-08	2013-Nov-07	- New target date: 2013-Oct-09 - Request for extension to embargo period received from manufacturer on 2013-Oct-04 - Extension to embargo period granted. - Embargo period extended to 2013-Nov-07
8 (c)	Placed on CDEC Agenda For Reconsideration (At Manufacturer's request)	25 Depends on Meeting Dates	2013-Nov-20		- New target date: 2014-Jan-15 - Submission voluntarily withdrawn by the manufacturer on 2013-Nov-12

Whats up in BC?

BRITISH COLUMBIA | Ministry of Health

BC PharmaCare Drug Information

Public input start date	Thursday October 17, 2013
Public input closing date	Thursday November 14, 2013 **AT MIDNIGHT.**

Cost of the drug under review compared to other drugs used to treat the same indication

generic name (Brand Name) of Drug Comparator	PharmaCare Status (if and how the drug is already covered)	Usual Dose	Daily Cost of Therapy
mirabegron (Myrbetriq™)	**Under Review**	**One tablet once daily**	**$1.73**
Oxybutynin (Ditropan®, generic)	Regular Benefit	One to two tablets daily	$0.32 to $0.64
Oxybutynin ER (Ditropan XL®)	Non-Benefit	One to two tablets daily	$2.34 to $7.02
Tolterodine (Detrol®)	Non-Benefit	One tablet daily	$2.06
Tolterodine ER (Detrol LA®)	Non-Benefit	One to two tablets daily	$2.07

So what?

Efficacy	Mortality	?
	Quality of Life	?
	# Episodes incontinence/day	~ ↓0.5/day @ 12 wks
	# Episodes nocturia/day	~ ↓0.4/day @ 12 months
	# Episodes of urge/day	~ ↓0.6/day @ 12 wks
	# Voids/day	~ ↓0.6/day @ 12 wks
Safety	SAE	Similar to tolterodine
	Withdrawals due to ADR	
	Total ADRs	
Benefits	↓cost vs. tolterodine	

Case: JM

- 77 year old male
  - Fall back on hospital formulary
  - Oxybutynin 2.5mg PO BID

- **When to trial Mirabegron:**
  - **ADRs to antimuscarinics**
  - **Patient willingness**

- **A trial of 4-12 weeks is recommended to assess efficacy**

A little extra...

ADR - Hypertension

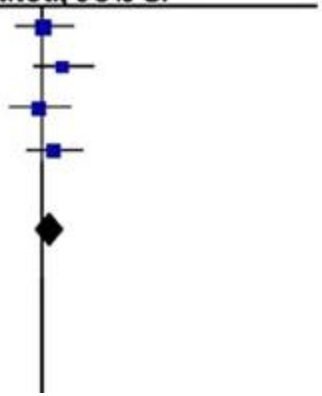
# of TEAE

(a)

Study or Subgroup	mirabegron Events	Total	placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
178-CL-048	93	380	91	379	26.8%	1.03 [0.74, 1.43]
ARIES	80	442	66	452	20.8%	1.29 [0.91, 1.85]
CAPRICORN	76	439	77	433	24.9%	0.97 [0.68, 1.37]
SCORPIO	100	492	89	494	27.5%	1.16 [0.84, 1.59]
Total (95% CI)		**1753**		**1758**	**100.0%**	**1.10 [0.93, 1.31]**
Total events	349		323			

Heterogeneity: Chi² = 1.58, df = 3 (P = 0.66); I² = 0%

Test for overall effect: Z = 1.15 (P = 0.25)



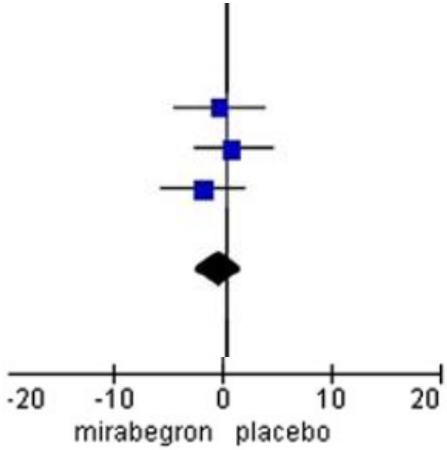
Hypertension events

(b)

Study or Subgroup	mirabegron Events	Total	placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ARIES	27	443	30	455	28.5%	0.92 [0.54, 1.57]
CAPRICORN	40	440	37	433	34.8%	1.07 [0.67, 1.71]
SCORPIO	29	497	38	497	36.7%	0.75 [0.45, 1.23]
Total (95% CI)		**1380**		**1385**	**100.0%**	**0.91 [0.68, 1.21]**
Total events	96		105			

Heterogeneity: Chi² = 1.05, df = 2 (P = 0.59); I² = 0%

Test for overall effect: Z = 0.65 (P = 0.52)



Int Urol Nephrol. 2013 Jul 30. [Epub ahead of print]

RCT – Chapple et al.

Appendix 3 – The five most frequently reported occurrences of medical history and comorbidities

MedDRA (v.9.1) preferred term, *n* (%)	Mirabegron 50 mg (*n* = 812)	Mirabegron 100 mg (*n* = 820)	Tolterodine ER 4 mg (*n* = 812)
Hypertension	348 (42.9)	351 (42.8)	372 (45.8)
Hysterectomy	145 (17.9)	156 (19.0)	184 (22.7)
Menopausal symptoms	167 (20.6)	155 (18.9)	156 (19.2)
Drug hypersensitivity	106 (13.1)	128 (15.6)	118 (14.5)
Depression	130 (16.0)	101 (12.3)	106 (13.1)

ER = extended release; MedDRA = Medical Dictionary for Regulatory Activities.
Data are for the safety analysis set.

Appendix 5 – Adjusted mean change from baseline to final visit in vital signs measured by patient's diary

	Mirabegron 50 mg (*n* = 812)		Mirabegron 100 mg (*n* = 820)		Tolterodine ER 4 mg (*n* = 812)	
Pulse rate, bpm						
AM	0.9 ± 0.23		1.6 ± 0.22		1.5 ± 0.22	
95% CI	0.5–1.4		1.2–2.1		1.1–2.0	
PM	0.4 ± 0.24		1.3 ± 0.24		1.9 ± 0.24	
95% CI	−0.1 to 0.8		0.8–1.7		1.4–2.4	
Blood pressure, mm Hg	SBP	DBP	SBP	DBP	SBP	DBP
AM	0.2 ± 0.33	−0.3 ± 0.21	0.4 ± 0.33	0.4 ± 0.20	−0.5 ± 0.33	0.1 ± 0.21
95% CI	−0.4 to 0.9	−0.7 to 0.1	−0.2 to 1.1	−0.0 to 0.8	−1.1 to 0.2	−0.3 to 0.5
PM	−0.3 ± 0.33	−0.0 ± 0.21	0.1 ± 0.32	0.1 ± 0.21	−0.0 ± 0.33	0.6 ± 0.21
95% CI	−0.9 to 0.3	−0.4 to 0.4	−0.5 to 0.8	−0.3 to 0.5	−0.7 to 0.6	0.2 to 1.0

DBP = diastolic blood pressure; ER = extended release; SBP = systolic blood pressure.
Data are for the Safety Analysis Set. All data are adjusted mean changes plus or minus standard error from baseline unless otherwise indicated.

Eur Urol. 2013 Feb;63(2):296-305.