Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Mirabegron

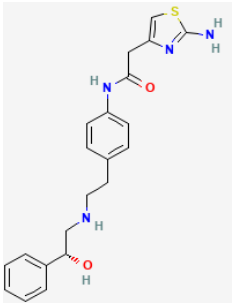
Evidence Summary

Mirabegron may improve glucose metabolism by facilitating the activation of brown fat, but the clinical impacts and therapeutic utility for cardiometabolic or neurodegenerative disorders is unclear.

Neuroprotective Benefit: Mirabegron shows a better therapeutic profile relative to anticholinergics in those with cognitive impairment because it does not facilitate decline. It may promote glucose utilization in the brain based on preclinical studies.

Aging and related health concerns: By activating brown fat, mirabegron can improve glucose metabolism. It may improve cardiac function at high doses, but the clinical data is mixed, as it can also increase blood pressure.

Safety: It shows good safety in clinical trials and real-world cohorts at doses approved for overactive bladder. It may increase blood pressure at higher doses and interact with medications that are metabolized by CYP2D6.

Availability: Rx	**Dose**: 25 mg or 50 mg/day as oral tablets for overactive bladder	**Chemical formula:** $C_{21}H_{24}N_4O_2S$ **MW**: 396.5 g/mol  Source: PubChem
Half-life: ~50 hours	**BBB**: low penetrance	
Clinical trials: Mirabegron has been tested for overactive bladder in a variety of populations, including large Phase 3 trials (12 weeks n=4,611 and 1-year n=1,632), and a Phase 4 trial (n=868). It has been tested in pilot studies for obesity (n=6, n=17, n=20, n=39) and heart failure (n=22, n=296).	**Observational studies**: Real-world cohorts indicate that mirabegron does not facilitate cognitive decline relative to anticholinergic overactive bladder medications.	

What is it?

Mirabegron is a beta-3 adrenergic receptor agonist [1]. The beta-3 adrenergic receptor is expressed on the human detrusor muscle of the bladder, which contracts to allow urination and relaxes to allow urine storage. Activation of this receptor promotes relaxation, and thus this class of drugs, including mirabegron, has been clinically tested for overactive bladder as an alternative to anticholinergic agents. Mirabegron is marketed under the tradename Myrbetriq® by Astellas Pharma and is FDA approved for the treatment of overactive bladder. Beta-3 adrenergic receptors are highly expressed on brown adipose tissue, which is involved in thermogenesis and promotes a favorable cardiometabolic profile [2]. Consequently, mirabegron has been tested for cardiac and metabolic conditions, such as left ventricular hypertrophy and obesity in pilot clinical trials. The doses required for benefit appear to be higher for these indications relative to the doses used for overactive bladder, however, more studies are needed to determine whether safe and effective doses can be found for cardiometabolic indications.

Neuroprotective Benefit: Mirabegron shows a better therapeutic profile relative to anticholinergics in those with cognitive impairment because it does not facilitate decline. It may promote glucose utilization in the brain based on preclinical studies.

Types of evidence:

- 1 phase 4 RCT for overactive bladder
- 1 pilot study for Parkinson's disease and overactive bladder
- 1 open-label trial for spinal cord injury and neurogenic bladder
- 2 observational studies in dementia patients for overactive bladder
- 1 observational study in patients with cerebrovascular diseases for overactive bladder
- 1 case study for Parkinson's disease and overactive bladder
- Several laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

Anticholinergic overactive bladder medications have been associated with cognitive decline [3], while beta-3 agonists, such as mirabegron, do not appear to significantly increase the risk for cognitive decline. To date, there is no evidence to indicate that mirabegron itself reduces the risk for cognitive decline, but it shows a lower relative risk profile in comparison with other overactive bladder medications.

In a population-based nested case-control study including 11,392 newly diagnosed dementia patients ≥ 66 years old in Ontario, Canada, prior use of mirabegron was associated with lower odds of developing dementia, relative to other overactive bladder medications [4]. Compared to patients receiving mirabegron six months to 12 months prior to diagnosis, patients receiving the anticholinergic solifenacin had higher odds of incident dementia (Odds ratio [OR] 1.34, 95% Confidence Interval [CI] 1.11 to 1.60). Similarly increased odds were seen for those receiving darifenacin (OR 1.49; 95% CI 1.19 to 1.86), tolterodine (OR 1.21; 95% CI 1.02 to 1.45), or fesoterodine (OR 1.39; 95% CI 1.14–1.71) relative to mirabegron.
The Phase 4 RCT (NCT02216214) assessed the impact of mirabegron (25 or 50 mg/day) for 12 weeks on cognitive function in 887 older adults (>65 years old) with overactive bladder [5]. In this population, all participants had at least one comorbidity and 94.3% were receiving a concomitant medication. Baseline cognitive impairment, based on a Montreal Cognitive Assessment (MoCA) score <26, was apparent in

27.1% (115/425) of mirabegron and 25.8% (106/411) of placebo group patients. At the end of the study, there was no significant change in cognition based on MoCA scores in the mirabegron (−0.2 ±0.1) or placebo groups (−0.1 ±0.1), suggesting that mirabegron does not significantly impact short-term cognition.

In an open label study of 20 older adults (>60 years old) with neurogenic lower urinary tract dysfunction and spinal cord injury, cognitive function was assessed in patients that were switched from an anticholinergic overactive bladder medication to mirabegron (25 mg) for six months [6]. Statistically significant improvements were seen on memory assessments in the Weschler Memory Scale IV (WMSIV), including immediate recall story A, and delayed recall Story A and B. Statistically significant improvements were also seen on the Telephone Executive Assessment Scale measure of executive function. However, significant improvements were not seen on the Saint Louis University Mental Status Exam, Symbol Digit Modality Test, or Stroop Color-Word Test, which are considered assessments of memory, executive function, and attention, respectively. Discrepancies may be due to differences in test sensitivity and the small sample size. Overall, it suggests that for older adults with bladder dysfunction, switching to mirabegron from anticholinergics may provide some cognitive benefit.

Human research to suggest benefits to patients with dementia:

Dementia: MIRABEGRON IS NOT ASSOCIATED WITH COGNITIVE IMPAIRMENT

In a retrospective cohort study of 540 dementia patients taking overactive bladder medication, the mortality risk was 55% higher (Hazard ratio [HR] 1.55, 95% CI 1.19 to 2.01) for patients taking medications with a high CNS anticholinergic burden relative to patients taking medications with low or no CNS anticholinergic burden, such as mirabegron [7]. Additionally, patients taking high anticholinergic burden medications showed a greater degree of cognitive decline over a 24-month period, with a decline of 1.88 points per year on the Mini-Mental State Examination (MMSE), while those taking low burden medications declined at a rate of 0.73 points per year.

However, the risk-benefit analysis for the use of these medications needs to consider not only the potential for cognitive side effects, but also efficacy. A cohort study of 102 older adults with CNS disorders, including cerebrovascular accident, Parkinson's disease, and dementia, assessed the efficacy and safety profile of the overactive bladder medications mirabegron 50 mg/day, solifenacin 5 mg/day, or the combination for three to six months [8]. No significant impact was seen on cognition over six months, based on the MMSE. Dementia patients showed less benefit on urinary measures relative to the other groups, suggesting that impaired cortical function may impact perceptions of bladder fullness, and thus limit the efficacy of these situations. While the efficacy was lower for mirabegron

monotherapy, the risk-benefit profile suggests that mirabegron may be the better therapeutic option in patients with CNS disorders.

Parkinson's disease: BENEFIT FOR OVERACTIVE BLADDER
Several pilot studies have assessed the feasibility of using mirabegron to treat overactive bladder in patients with Parkinson's disease (PD). In one study, seven out of 30 PD patients taking mirabegron (50 mg/day) for three months achieved complete urinary continence, while 24 showed significant benefit on urinary incontinence quality of life measures [9]. There were no discontinuations due to side effects. In an RCT comparing mirabegron (50 mg) with placebo in PD patients (n=110), 72% mirabegron-treated patients reached the minimal clinically important difference of a three-point change in the overactive bladder symptom score (OABSS) by the end of 12 weeks, compared to none in the placebo group [10]. A study testing mirabegron (50 mg/day) alone or in combination with solifenacin (5 mg/day), included 25 PD patients, and found that in this population, mirabegron improved OABSS and measures of urinary incontinence [8]. Additionally, mirabegron monotherapy was associated with fewer adverse events relative to solifenacin.
However, there is a case report implicating mirabegron in sudden onset dyskinesia in a 72-year-old woman with PD for 19 years [11]. She had a history of severe dyskinesia that was well-managed by globus pallidus internus deep brain stimulation at the time of the event. The onset of dyskinesia coincided with the start of mirabegron and subsided within 24-hours of cessation. It is hypothesized that the modulation of serotonin or noradrenaline neurotransmission by mirabegron may have accounted for the effect. Emergent dyskinesia was not seen in PD patients treated with mirabegron in the pilot clinical trials, so it is unclear whether there is a particular subset of patients, such as those with implanted stimulators, who may be most susceptible to mirabegron-associated adverse events.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Improved glucose metabolism: Mirabegron has been shown to improve peripheral glucose metabolism in both humans and rodents. In the 3x-Tg AD mouse model, treatment with the beta-3 adrenergic agonist CL-316,243 for one month starting at 15 months of age, which is late in the disease course, when cognitive deficits are apparent, increased recognition on the novel object recognition task by 19%, while cognition was not affected in non-transgenic mice [12]. The impact on cognition was correlated with the activation of brown adipose tissue, based on levels of UCP1. Mitochondrial complex I activity increased, and hippocampal levels of insoluble Aβ42/40 decreased by 27% in this model. Since CL-316,243 does not readily cross the BBB, these effects appear to be mediated by improvements to peripheral metabolic

parameters, and suggest that at doses which promote brown and beige adipocyte activation, mirabegron may also provide indirect metabolic benefits to the brain.
Additionally, unlike CL-316,243, mirabegron is weakly BBB penetrant, and thus may have direct effects through the activation of CNS beta-3 adrenergic receptors. Beta-3 adrenergic receptor knockout mice have decreased brain expression of the glucose transporter GLUT3, indicative of decreased glucose utilization, which is accompanied by deficits in memory formation [13]. Similarly, treatment of day-old chicks with CL-316243 facilitated both glucose utilization via GLUT3 and memory enhancement [14]. Mirabegron also mitigated scopolamine-induced memory impairment in mice. While the expression of beta-3 adrenergic receptor in the rodent brain is only around 0.2-3%, depending on the brain region, relative to brown adipose tissue, a study in male rats found that intravenous administration of mirabegron could increase glucose utilization in the brain, based on 18F-FDG PET imaging [15]. The effect was highest in the frontal cortex, which is the brain region with higher beta-3 adrenergic receptor expression. This suggests that mirabegron could potentially increase glucose utilization in the brain, though the effects are likely to be heterogenous across brain regions, and the dose required to achieve this effect in humans has not been established.

Neurogenesis: It has not been established whether mirabegron specifically promotes hippocampal neurogenesis, but there is evidence that activation of CNS beta-3 adrenergic receptors via BBB penetrant beta-adrenergic receptor agonists or physiological stimuli, such as cold exposure, can increase levels of neural progenitor cells in the hippocampus of rodents [16]. This is a direct CNS effect, as it is not seen with the use of the non-CNS penetrant beta-3 adrenergic receptor agonist, CL-316,243. It is not clear whether a similar effect occurs in humans, and if so, whether it could be achieved by a therapeutically safe dose of mirabegron.

Anti-depressant: Anti-depressant effects have been reported with the activation of CNS beta-3 adrenergic receptors in rodents. Mirabegron has been shown to reduce depression-like behavior in mice [17]. However, the CNS-penetrant beta-3 adrenergic receptor agonist, amibegron, also showed anti-depressant activity in rodents, but its clinical development was discontinued due to lack of efficacy in clinical trials.

APOE4 interactions: Not established

Aging and related health concerns: By activating brown fat, mirabegron can improve glucose metabolism. It may improve cardiac function at high doses, but the clinical data is mixed, as it can also increase blood pressure.

Types of evidence:

- 4 clinical trials for metabolic parameters
- 2 clinical trials for heart failure
- Numerous laboratory studies

Obesity: POTENTIAL BENEFIT

Brown adipose tissue is mitochondria rich, metabolically active fat tissue involved in thermoregulation [18]. This tissue can generate heat through mitochondrial uncoupling, whereby the proton gradient in mitochondria becomes uncoupled from energy production and instead releases heat. The activation of brown adipose tissue results in increased energy expenditure, and has been associated with improved glucose homeostasis and insulin sensitivity. Consequently, brown adipose tissue activation has been proposed as a strategy to combat metabolic disorders, such as diabetes and obesity. Brown adipose tissue is innervated by the sympathetic nervous system, and thus is regulated by certain sympathetic activating stimuli. The receptor responding to the sympathetic stimuli is the beta-3 adrenergic receptor, thus activation of this receptor can also trigger brown fat activation. Brown adipose tissue is abundant in newborns, and levels decrease with age, such that adipose tissue is primarily of the white variety, which is utilized for fat storage, in adults. Due to the small amount of brown fat in humans, its activation may not be as potent for metabolic regulation as is seen in rodent studies. Within white adipose tissue, there are dormant beige adipocytes, which are similar to brown adipocytes in that they are involved in thermogenesis [19]. Additionally, white adipocytes can be transformed into beige adipocytes under certain conditions. Beige adipocytes become activated in response to beta-3 adrenergic receptor activating stimuli, such as cold exposure. Thus, beige adipocyte activation may play a greater role in beta-3 adrenoreceptor-mediated lipolysis. Additionally, a hypofunctional genetic variant in the beta-3 adrenergic receptor, Trp64Arg, has been implicated in increased susceptibility to metabolic disorders [2]. As a beta-3 adrenoreceptor agonist, mirabegron has the potential to activate brown and beige adipose tissue. However, it can also potentiate other aspects of the sympathetic nervous system, such as cardiovascular effects, at high doses. Several clinical studies have been conducted to try to determine dose ranges that can be safely used to activate brown and beige adipose tissue.

The impact on metabolic parameters of mirabegron has been assessed in clinical studies in both lean and obese subjects. In 17 healthy adults without cardiometabolic diseases participating in an ascending dose study from 50 to 200 mg of mirabegron, energy expenditure increased at doses ≥100 mg (+35.6 kJ/h) [20]. Similarly, supraclavicular skin temperature, a surrogate measure for brown adipose tissue activation, also increased at doses between 50 mg (+0.22 ± 0.1°C) and 150 mg (+0.29 ± 0.1°C). Sympathomimetic features, such as an increase in systolic blood pressure (+9.3 ± 1.9 mm Hg) and heart rate (+9.0 ± 2.2 bpm) were observed at the 200 mg dose, suggesting that 100 mg may be the optimal dose to promote brown fat activation.

The induction of dormant beige adipocytes was assessed in six obese, insulin-resistant subjects treated with mirabegron (50 mg/day) for ten weeks [21]. The induction of mitochondrial uncoupling proteins, such as UCP1, drives a thermogenic response whereby mitochondrial activity produces heat instead of creating ATP. Mirabegron treatment increased levels of UCP1 by three-fold and led to the induction of beige adipose markers, TMEM26 by 8.7-fold, and CIDEA by 3.4-fold in subcutaneous abdominal white adipose tissue. This is a higher degree of induction than was seen with ten days of cold exposure. Mechanistically, mirabegron treatment induced the activation of hormone-sensitive lipase (HSL), which is involved in the mobilization of stored fats, via phosphorylation on residue serine 660 by protein kinase A (PKA). Unlike in rodents, mirabegron treatment did not lead to the activation of PGC-1α, a regulator of mitochondrial biogenesis and the adipose tissue beiging response in this study. However, elevated adipose tissue inflammation, as often occurs in the context of obesity, has been shown to inhibit the PGC-1α activation. Thus, the response of mirabegron on mitochondria may vary based on levels of inflammation, or tissue type.

In an RCT including 39 obese (BMI >27) participants, treatment with mirabegron (50 mg/day) for 12 weeks also promoted the induction of beige adipose tissue-associated markers in abdominal subcutaneous white adipose tissue, UCP1 by 2.4-fold, TMEM26 by 4.2-fold, and CIDEA by 2.4-fold [22]. In skeletal muscle, mirabegron treatment increased the number of type 1 muscle fibers, reduced levels of triglycerides, and promoted the expression of PGC-1α. Conditioned media from mirabegron-treated adipocytes similarly induced the expression of PGC-1α in cultured muscle fibers. Clinically, the subset of participants with impaired glucose tolerance at baseline showed improved oral glucose tolerance, with a decrease in 120-minute glucose levels from 165 mg/dl to 120 mg/dl. Additionally, there were improvements in HbA1c levels and insulin sensitivity, such that five of the nine mirabegron-treated prediabetic subjects were no longer classified as prediabetic based on American Diabetes Association criteria by the end of the study. The improvement in pancreatic beta-cell function was correlated with the degree of adipose tissue beiging, suggesting that the metabolic effects were attributable to that activity of mirabegron in adipose tissue.

A clinical study assessed the metabolic effects of a single oral dose of mirabegron (200 mg) in 10 South Asian men and 10 Caucasian men [23]. Levels of total cholesterol, triglycerides, LDL-c, or HDL-c were not significantly impacted by a single dose of mirabegron, suggesting that at least in the short term, mirabegron does not impact the serum lipid profile in the same manner as cold exposure. Mirabegron similarly increased free fatty acids in the South Asian (+155%) and Caucasian (+214%) groups, and increased insulin levels, by 38% and 23%, respectively, without affecting glucose levels. Mirabegron also increased the supraclavicular skin temperature, which is likely an indication of brown adipose tissue activation, since it was coupled with a decrease (-1.4%) in this fat fraction.

Atherosclerosis: UNCLEAR
In preclinical models of atherosclerosis, mirabegron treatment has been shown to exacerbate atherosclerotic plaque development and instability [24; 25]. However, this effect may stem from the defects in cholesterol clearance that characterize these models. The increase in free fatty acids stemming from brown adipose tissue activation typically leads to the generation of cholesterol-rich lipoprotein remnants, which are then taken up by the liver via the ApoE-Ldlr pathway, which is generally considered atheroprotective [24]. In models where this pathway is defective, LDL-c is not cleared effectively, and instead accumulates, promoting plaque growth. Additionally, brown adipose tissue activation is more robust in rodents. Overall, these studies suggest that individuals with dysfunction in the ApoE-Ldlr pathway may be susceptible to an atherosclerotic effect, but this effect is unlikely to be apparent in the majority of individuals.

Heart failure: NO CLEAR BENEFIT AT LOW DOSES
Mirabegron was tested in a phase 2b placebo controlled RCT in patients with left ventricular hypertrophy with no or mild (NYHA II) symptoms of heart failure (NCT02599480). Participants (n=296) were treated with 50 mg/day mirabegron or placebo for 12 months. It was reported at the 2022 American Heart Association Scientific Sessions, that the study did not meet its primary endpoint of preventing the advancement of structural heart damage (Press release). Relative to placebo, the left ventricular mass index changed by +1.3 g/m2 (95% CI -0.15 to 2.74), while diastolic function changed by -0.15 E/e' (95% CI -0.69 to 0.4), though neither of these changes were statistically significant. Secondary outcomes on cardiac parameters were also not significantly affected by treatment. However, while the safety of mirabegron in those with cardiovascular risk factors was strong at the tested dose, it may have been too low to exert clinically meaningful effects. In a small RCT, patients (n=22) with heart failure with reduced ejection fraction (NYHA functional class III-IV) received mirabegron (300 mg/day) or placebo for one week as an add-on to their standard therapy [26]. Relative to placebo, one week of mirabegron

treatment significantly increased the cardiac index, an assessment of cardiac output, (mean difference 0.41 L/min/BSA, 95 % CI, 0.07 to 0.75), and decreased pulmonary vascular resistance (mean difference −1.6 Wood units, 95% CI −0.4 to −2.8). Heart rate, blood pressure, systemic vascular resistance, and renal function were not significantly affected. In addition to the higher dose used in this study, the later stage patients may have preferentially benefited since the expression of the beta-3 adrenoreceptor is elevated in later stages of heart failure, and thus may be more susceptible to modulation. Overall, these studies suggest that the standard dose of 50 mg mirabegron used for overactive bladder may be ineffective for protecting against adverse cardiac remodeling, but as long as cardiovascular side effects can be avoided, higher doses could potentially be cardioprotective.
Within the myocardium, beta-3 adrenergic receptor activity can increase nitric oxide production via the induction of endothelial nitric oxide synthase [2]. While the expression is typically low under physiological conditions, it becomes elevated under pathophysiological conditions. Preclinically, exosomes derived from mirabegron-treated adipocytes reduced cardiac dysfunction in an angiotensin II-induced mouse model of cardiac remodeling [27]. The cardioprotective effects were associated with the beta-3 adrenoceptor-mediated inhibition of inducible nitric oxide synthase in brown adipocytes. This suggests that the profile of adipocyte-secreted factors impacts cardiac function, and the adipocyte secretome can be influenced by beta-3 adrenoreceptor activity.

Safety: It shows good safety in clinical trials and real-world cohorts at doses approved for overactive bladder. It may increase blood pressure at higher doses and interact with medications that are metabolized by CYP2D6.

Types of evidence:

- 1 systematic review of studies assessing ocular adverse events
- 1 systematic review of trials in spinal cord injury or multiple sclerosis patients
- 4 clinical trials for metabolic parameters
- 2 clinical trials for heart failure
- 1 phase 4 RCT for overactive bladder
- 1 pilot studies for Parkinson's disease and overactive bladder
- 1 clinical trial assessing the impact to the retina and choroid
- 3 real-world cohorts assessing cardiovascular risk
- 1 case study for Parkinson's disease and overactive bladder
- Numerous laboratory studies

Mirabegron has generally been well-tolerated in clinical trials at the approved dosages of 25 and 50 mg. In these trials, the most commonly reported adverse events were hypertension, nasopharyngitis, urinary tract infection, and headache [28]. The FDA prescribing label provides warnings against use in patients with severe uncontrolled hypertension and in patients with bladder outlet obstruction. In the Phase IV PILLAR RCT testing 25 to 50 mg/day mirabegron for 12 weeks in 868 participants (≥65 years old), the most common treatment-emergent adverse events for mirabegron patients were urinary tract infection, headache, and diarrhea [29]. Cognition, based on the MoCA score, was not significantly impacted, and none of the adverse events results in death.

Cardiovascular: NO INCREASED RISK FOR MAJOR CARDIOVASCUKAR EVENTS

Although increases in blood pressure and heart rate were observed in clinical trials, particularly at high doses, real-world cohort data suggests that mirabegron does not significantly increase the risk for adverse cardiovascular events in individuals with or without cardiovascular risk factors [30]. An analysis of adverse events in the Eudra-Vigilance database stemming from overactive bladder medication, including 7,213 for mirabegron, found that hypertension was more commonly reported for mirabegron (7%) relative to anticholinergics (1-2%), and was more prevalent in women. In trials using mirabegron for neurogenic bladder in patients with spinal cord injury or multiple sclerosis, one study reported a patient with tachyarrhythmia, while another reported a patient with tachycardia [31].

In healthy individuals without overactive bladder, doses of mirabegron between 25 and 100 mg did not result in increased rates of tachycardia, blood pressure, or ECG measures. At a dose of 200 mg, mirabegron acutely increased heart rate in healthy men by 7 to 10 beats/min.

In a population-based cohort in Ontario, Canada including 38, 818 older adults (≥66 years old) taking overactive bladder medication, the use of mirabegron was not associated with an increased risk for myocardial infarction or stroke relative to other medications for overactive bladder (HR: 1.06; 95% CI, 0.89 to 1.27) [32]. The incidence of arrhythmia or tachycardia was also similar for mirabegron (3.6%) relative to other overactive bladder medications (3.8%). Notably, cardiovascular risk factors, such as hypertension (78.3%) and diabetes (35.4%), were prevalent in this cohort. A separate cohort study analyzed real-world data from five databases including 152,026 mirabegron users and 152,026 anticholinergic users with overactive bladder, approximately 70% of which were deemed to be at high risk for cardiovascular events [30]. Incidence rates for major cardiovascular adverse events, acute myocardial infarction, or stroke, were similar between mirabegron users relative to users of other overactive bladder medications. Incidence of cardiovascular mortality (HR: 0.83, 95% CI 0.73 to 0.95)

and all-cause mortality (HR: 0.80, 95% CI 0.76 to 0.84) was lower with mirabegron use relative to the use of anticholinergics.

Ocular: RISK FOR OCULAR SYMPTOMS AT HIGH DOSES
In a systematic review of 23 studies assessing 422 vision-related adverse events from 8,459 patients taking overactive bladder medication, mirabegron was associated with ocular symptoms from the most categories, including blurred vision, glaucoma, conjunctivitis, iritis, uveal tract infection, other eye disorders [33]. However, mirabegron was less likely to be associated with severe vision adverse events, and the incidence rates of these mild to moderate events were all less than 10%, and highly dose related, with ocular symptoms emerging at the highest doses. Meanwhile, a prospective case-control study assessed the effect of 50 mg mirabegron on retinal thickness and choroidal vascularity in the eyes of 26 participants [34]. Mirabegron influenced the choroidal vascular response via expansion in the Haller's layer, suggesting it may have therapeutic utility in ocular vascular disorders.

Anticholinergic burden: POTENTIAL IMPACT IN COMBINATION
The use of mirabegron on its own does not appear to appreciably induce anticholinergic-related symptoms, and has been associated with lower overactive bladder-related comorbidities requiring medical care [35]. However, mirabegron is approved for use as a monotherapy or in combination with the anticholinergic solifenacin. When used in combination, the incidence of anticholinergic side effects, such as dry mouth, constipation, and blurred vision, is higher relative to solifenacin alone, suggesting that mirabegron may be contributing to these effects [36]. Indeed, mirabegron has been reported to show binding affinity to human M2 muscarinic receptors (Ki value of 2.1 μM). In bladder tissue from rats, mirabegron was able to reverse muscarinic acetylcholine receptor mediated contraction. Based on this study and pharmacokinetic data, the muscarinic receptor occupancy in the human bladder following a 50 mg dose of mirabegron is estimated to be 37%–76% [36]. This suggests that mirabegron could contribute to anticholinergic burden when used in combination with other drugs with anticholinergic activity, which may impact the side effect profile.

Drug interactions:

According to Drugs.com, there are 218 drugs that interact with mirabegron, eight of which are major interactions, including, berotralstat, brexpiprazole, eliglustat, oliceridine, pimozidem, tamoxifen, thioridazine, and venetoclax. Mirabegron is a moderate quasi-irreversible, metabolism-dependent inhibitor of the CYP450 enzyme, CYP2D6, and thus impacts the metabolism of other drugs that utilize

CYP2D6, and can result in elevated levels [37]. Mirabegron also has a minor interaction with food, such that food reduces the oral bioavailability of mirabegron, but the effect is not large enough to warrant dosing recommendations with or without food (Drugs.com).

Sources and dosing:

Mirabegron is marketed under the brand name Myrbetriq® by Astellas Pharma as extended-release tablets at dosages of 25 mg or 50 mg taken orally once per day for patients with overactive bladder. In clinical trials assessing the use of mirabegron for obesity and metabolic disorders, effects were seen with 50 mg/day, but doses between 100-200 mg/day showed more consistent effects [20; 22]. Similarly, a dose of 50 mg/day was insufficient to prevent adverse cardiac remodeling, but higher doses, such as 300 mg/day, show the potential to be more effective [26]. Though side effects are generally more apparent at the higher doses.

Research underway:

According to Clinicaltrials.gov, there are currently 27 active trials for mirabegron. These studies are for overactive bladder, neurogenic detrusor overactivity, intracerebral hemorrhage, obesity/prediabetes, polycystic ovary syndrome, and thermogenesis.

Search terms:
Pubmed, Google: Mirabegron

- Alzheimer's disease, dementia, cognition, cardiovascular, mortality, obesity, clinical trial, meta-analysis, systematic review, safety

Websites visited for Mirabegron:

- Clinicaltrials.gov
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca
- Cafepharma

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