

## **SUMMARY OF PRODUCT CHARACTERISTICS**

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

### **1 NAME OF THE MEDICINAL PRODUCT**

Obgemsa 75 mg film-coated tablets.

### **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each film-coated tablet contains 75 mg of vibegron.

Excipient with known effect

Each film-coated tablet contains 1.5 mg of lactose.

For the full list of excipients, see section 6.1.

### **3 PHARMACEUTICAL FORM**

Film-coated tablet (tablet).

Light green oval film-coated tablet, debossed with V75 on one side and plain on the other side. Tablet dimension is approximately 9 mm (length) x 4 mm (width) x 3 mm (height).

### **4 CLINICAL PARTICULARS**

#### **4.1 Therapeutic indications**

Obgemsa is indicated in symptomatic treatment of adult patients with overactive bladder (OAB) syndrome.

## **4.2 Posology and method of administration**

### Posology

The recommended dose is 75 mg once daily.

### Special populations

#### *Renal impairment*

No dose adjustment for vibegron is recommended for patients with mild, moderate, or severe renal impairment ( $15 \text{ mL/min} < \text{GFR} < 90 \text{ mL/min}$  and not requiring dialysis). Vibegron has not been studied in patients with end-stage renal disease ( $\text{GFR} < 15 \text{ mL/min}$  with or without haemodialysis) and is therefore not recommended in these patients (see section 5.2).

#### *Hepatic impairment*

No dose adjustment for vibegron is recommended for patients with mild to moderate hepatic impairment (Child-Pugh A and B). Vibegron has not been studied in patients with severe hepatic impairment (Child-Pugh C) and is therefore not recommended in this patient population (see section 5.2).

### Paediatric population

The safety and efficacy of vibegron in children below 18 years of age have not yet been established.

No data are available.

### Method of administration

Oral administration, with or without food. Swallow with a glass of water.

Obgemsa 75 mg film-coated tablets may also be crushed, mixed with a tablespoon (approximately 15 mL) of soft food (e.g. applesauce) and taken immediately with a glass of water.

### 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

### 4.4 Special warnings and precautions for use

#### Patients with bladder outlet obstruction and patients taking antimuscarinics medicinal products for OAB

Urinary retention has been reported in patients taking vibegron. The risk of urinary retention may be increased in patients with bladder outlet obstruction and also in patients taking muscarinic antagonist medicinal product concomitantly with vibegron treatment. Signs and symptoms of urinary retention should be monitored before and during the treatment with vibegron, particularly in patients with clinically significant bladder outlet obstruction, in patients with conditions predisposing for bladder outlet obstruction, and in patients taking muscarinic antagonist medicinal product concomitantly with vibegron.

Vibegron should be discontinued in patients who develop urinary retention.

#### Excipients

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

### 4.5 Interaction with other medicinal products and other forms of interaction

Vibegron is a substrate for cytochrome P450 (CYP) 3A4, multiple UGT enzymes and the efflux transporter P-glycoprotein (P-gp).

#### Medicinal products affecting the exposure of vibegron

*CYP3A4/P-gp inhibitors*

Vibegron exposure (AUC) was increased 2.1--and 1.6-fold in the presence of the strong and moderate inhibitor of CYP3A/P-gp ketoconazole and diltiazem, respectively, in healthy volunteers. No dose-adjustment is needed when vibegron is combined with strong and moderate inhibitors of CYP3A and/or P-gp.

#### *CYP3A4/P-gp inducers*

Vibegron AUC was not affected by repeat-dose administration of rifampicin, a strong inducer of CYP3A/P-gp, in healthy volunteers, while vibegron  $C_{max}$  was 86% higher. No dose adjustment is needed for vibegron when administered with CYP3A or P-gp inducers.

#### Effect of vibegron on other medicinal products.

A single dose of 100 mg vibegron increased  $C_{max}$  and AUC by 21% and 11%, respectively, of the P-gp substrate digoxin in healthy volunteers. Serum digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect.

The potential for interaction with P-gp by vibegron should be considered when combined with sensitive P-gp substrates with narrow therapeutic index e.g. dabigatran etexilate, apixaban or rivaroxaban.

Vibegron is an inhibitor of OCT1 *in vitro*. This interaction has not been studied *in vivo* and the clinical relevance is currently unknown.

#### Pharmacodynamic interactions

Co-administration of vibegron with metoprolol, a representative beta-blocker, or amlodipine, a representative vasodilator, did not result in a clinically meaningful decrease or increase in systolic blood pressure (SBP) relative to metoprolol alone or amlodipine alone.

#### Paediatric population

Interaction studies have only been performed in adults.

## **4.6 Fertility, pregnancy and lactation**

#### Women of childbearing potential

Vibegron is not recommended in women of childbearing potential not using contraception.

### Pregnancy

There are no or limited amount of data from the use of vibegron in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Vibegron is not recommended during pregnancy. When pregnancy is planned or diagnosed, treatment with vibegron should be stopped and, if appropriate, alternative therapy should be started.

### Breast-feeding

It is unknown whether vibegron/metabolites are excreted in human milk.

Available non-clinical data in animals have shown excretion of vibegron/metabolites in milk (see section 5.3).

A risk to the newborns/infants cannot be excluded.

Vibegron should not be used during breast-feeding.

### Fertility

The effect of vibegron on human fertility has not been established. Studies in animals have not shown effects on female or male rat fertility (see section 5.3).

## **4.7 Effects on ability to drive and use machines**

Obgemsa has no or negligible influence on the ability to drive and use machines.

## **4.8 Undesirable effects**

### Summary of the safety profile

The most frequently reported adverse reactions include urinary tract infection (6.6%), headache (5.0%), diarrhoea (3.1%) and nausea (3.0%).

The frequency of adverse drug reactions that led to treatment discontinuation is 0.9%. The most common adverse reactions leading to treatment discontinuation are: headache (0.5%), constipation, diarrhoea, nausea and rash (0.2% each).

### Tabulated list of adverse reactions

The table below reflects the adverse reactions observed with vibegron obtained from the phase 3 12-week study, phase 3 long-term extension study and post-marketing data.

The frequency of adverse reactions is defined as follows: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1\ 000$  to  $< 1/100$ ); rare ( $\geq 1/10\ 000$  to  $< 1/1\ 000$ ); very rare ( $< 1/10\ 000$ ) and not known (cannot be established from the available data).

**Table 1: Adverse reactions reported for vibegron 75 mg**

<b>System organ class</b>	<b>Adverse reaction</b>	<b>Frequency</b>
Infections and infestations	Urinary tract infection	Common
Nervous system disorders	Headache	Common
Vascular disorders	Hot flush	Uncommon
Gastrointestinal disorders	Constipation, Diarrhoea, Nausea	Common
Skin and subcutaneous tissue disorders	Rash <sup>a</sup>	Uncommon
Renal and urinary disorders	Urinary retention <sup>b</sup>	Uncommon
Investigations	Residual urine volume increased	Common

<sup>a</sup> includes rash pruritic and rash erythematous

<sup>b</sup> includes urinary straining

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: <https://yellowcard.mhra.gov.uk/> or search for MHRA Yellow Card in the Google Play or Apple App Store.

## **4.9 Overdose**

The cases of overdose have been reported in a dose range between 100 and 375 mg per day. All observed adverse events following the reported overdose were non-serious. The reported adverse events were gastrointestinal disorders, headache and dyspnoea.

In case of suspected overdose, treatment should be symptomatic and supportive.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urologicals, Drugs for urinary frequency and incontinence, ATC code: G04BD15.

#### Mechanism of action

Vibegron is a selective and potent human beta-3 adrenergic receptor agonist over  $\beta$ 1-AR and  $\beta$ 2-AR. Activation of the beta-3 adrenergic receptor located in the bladder detrusor muscle increases bladder capacity by relaxing the detrusor smooth muscle during bladder filling.

#### Clinical efficacy and safety

The efficacy of vibegron 75 mg was evaluated in a phase 3, 12-week, double-blind, randomised, placebo-controlled, and active-controlled trial (EMPOWUR) in OAB patients with symptoms of urgency and urinary frequency with or without urge urinary incontinence (UUI). Patients were randomised 5:5:4 to receive either vibegron 75 mg, placebo, or tolterodine ER 4 mg orally, once daily for 12 weeks. For study entry, patients had to have symptoms of OAB for at least 3 months with an average of 8 or more micturitions per day and at least 1 UUI per day, or an average of 8 or more micturitions per day and an average of at least 3 urgency episodes per day. UUI was defined as leakage of urine of any amount because the patient felt an urge or need to urinate immediately. The study population included OAB medicinal product-naïve patients as well as patients who had received prior therapy with OAB medicinal product. A total of 1 518 patients were randomised: 547 subjects were randomised to the vibegron group, 540 to the placebo group, and 431 to the tolterodine group. Of these 1 518 patients, 54 patients (10.0%) administered with placebo and 45 patients (8.2%) in the vibegron 75 mg group discontinued from the study. The main reason for study discontinuation was consent withdrawal (3.9% in the placebo group and 2.6% in the vibegron group).

The co-primary endpoints were change from baseline in average daily number of micturitions and average daily number of UUI episodes at Week 12. Important secondary endpoints included change from baseline in average daily number of urgency episodes, average daily number of total incontinence episodes, average

volume voided per micturition, % of patients with  $\geq 75\%$  and 100% reduction in the average daily number of UUI episodes, and Overactive Bladder Questionnaire Long Form (OAB-q LF) coping domain score.

A total of 1 515 patients received at least one daily dose of placebo (n=540), vibegron 75 mg (n=545), or active control (n=430). The majority of patients were Caucasian (78%) and female (85%) with a mean age of 60 (range 18 to 93) years, 77% patients presenting with UUI (OAB Wet). The percentage of patients at baseline over 65 years of age was 42.6% and over 75 years of age was 12.1%.

Vibegron 75 mg was effective in treating the symptoms of OAB within 2 weeks and efficacy was maintained throughout the 12-week treatment period (results are presented below in Table 2).

**Table 2: Mean baseline and change from baseline at week 12 for frequency of micturition, urge urinary incontinence episodes, urgency episodes, total incontinence episodes, and volume voided per micturition**

Parameter	Placebo	Vibegron 75 mg	Tolterodine ER 4 mg
<b>Average daily number of micturitions<sup>a</sup></b>			
Baseline mean (n)	11.8 (520)	11.3 (526)	11.5 (417)
Change from baseline <sup>b</sup> (n)	-1.3 (475)	-1.8 (492)	-1.6 (378)
Difference from placebo	-0.5		-0.3
95% Confidence Interval	-0.8, -0.2		-0.6, 0.1
p-value	<0.001 <sup>d,e</sup>		0.0988
<b>Average daily number of UUI episodes<sup>c</sup></b>			
Baseline mean (n)	3.5 (405)	3.4 (403)	3.4 (319)
Change from baseline <sup>b</sup> (n)	-1.4 (372)	-2.0 (383)	-1.8 (286)
Difference from placebo	-0.6		-0.4
95% Confidence Interval	-0.9, -0.3		-0.7, -0.1
p-value	<0.0001 <sup>d,e</sup>		0.0123
<b>Average daily number of “need to urinate immediately” (urgency) episodes<sup>a</sup></b>			
Baseline mean (n)	8.1 (520)	8.1 (526)	7.9 (417)
Change from baseline <sup>b</sup> (n)	-2.0 (475)	-2.7 (492)	-2.5 (378)
Difference from placebo	-0.7		-0.4
95% Confidence Interval	-1.1, -0.2		-0.9, 0.0
p-value	0.002 <sup>d,e</sup>		0.0648
<b>Average daily number of total incontinence episodes<sup>c</sup></b>			
Baseline mean (n)	4.2 (405)	4.1 (403)	4.1 (319)
Change from baseline <sup>b</sup> (n)	-1.6 (372)	-2.3 (383)	-2.0 (286)
Difference from placebo	-0.7		-0.5
95% Confidence Interval	-1.0, -0.4		-0.8, -0.1

Interval			
p-value	<0.0001 <sup>d, e</sup>		0.0074
<b>Average volume voided (mL) per micturition<sup>a</sup></b>			
Baseline mean (n)	148 (514)	155 (524)	147 (415)
Change from baseline <sup>b</sup> (n)	2 (478)	24 (490)	16 (375)
Difference from placebo	21		13
95% Confidence Interval	14, 28		9, 22
p-value	<0.0001 <sup>d, e</sup>		<0.001
<sup>a</sup> FAS-population: Full analysis set. All randomised patients with OAB who took at least 1 dose of double-blind study treatment and had at least one evaluable change from baseline micturition measurement. <sup>b</sup> Least squares mean adjusted for treatment, baseline, OAB type (only for analyses on FAS), gender, geographical region, study visit, and study visit by treatment interaction term. <sup>c</sup> FAS-I population: used for incontinence endpoints and included patients in the FAS population with OAB Wet at study entry who had at least 1 evaluable change from baseline UUI measurement. <sup>d</sup> Statistically significant. <sup>e</sup> Parameters included in the multiple testing procedure. Hypothesis testing was only performed for vibegron-placebo.			

Additional key secondary endpoints included the proportion of patients with a reduction at week 12 compared to baseline in average daily number of UUI episodes of  $\geq 75\%$  or  $100\%$ . Results are presented below (Table 3).

**Table 3: Secondary efficacy analysis: urge urinary incontinence 75% and 100% responder analysis at week 12 – FAS-I (included patients in the FAS population with OAB Wet at study entry who had at least 1 evaluable change from baseline UUI measurement)**

Statistic	Placebo N=405	Vibegron 75 mg N=403	Tolterodine ER 4 mg N=319
<b>Subjects with at least 75% reduction in UUI from baseline at week 12</b>			
Estimated* n (%)	133 (32.8)	199 (49.3)	135 (42.2)
<b>Active-Placebo<sup>a</sup></b>			
CMH Difference		16.5	9.4
95% CI		[9.7; 23.4]	[2.1; 16.7]
p-value		< 0.0001 <sup>b, c</sup>	0.0120
<b>Patients with 100% reduction in UUI from baseline at week 12</b>			
Estimated* n (%)	77 (19.0)	102 (25.3)	67 (20.9)
<b>Active-Placebo<sup>a</sup></b>			
CMH Difference		6.3	1.9
95% CI		[0.4; 12.1]	[-4.1; 7.8]
p-value		0.0360 <sup>b, c</sup>	0.5447

Notes: MI was used to impute values missing for any reason at the weeks analysed.

Presented frequencies and the denominator used for percentage were based on subjects in the FAS-I and randomised treatment.

\*The estimated proportion uses the SAS procedure MIANALYZE with standard multiple imputation effect estimation.

<sup>a</sup> The difference in proportion and corresponding CI and p-value was calculated using the Cochran-Mantel-Haenszel risk difference estimate stratified by sex (female vs male), with weights proposed by Greenland and Robins.

<sup>b</sup> Statistically significant.

<sup>c</sup> Comparisons included in the multiple testing procedure. Comparisons between tolterodine ER and placebo are considered descriptive.

The long-term safety and efficacy of vibegron 75 mg was evaluated for up to 52 weeks in a phase 3 extension study in 505 patients who had completed the 12-week phase 3 study (EMPOWUR).

### Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Obgemsa in one or more subsets of the paediatric population in the treatment of neurogenic detrusor overactivity (see section 4.2 for information on paediatric use).

## **5.2 Pharmacokinetic properties**

### Absorption

Mean vibegron  $C_{max}$  and AUC increased in a greater than dose-proportional manner up to 600 and 400 mg after single and repeated dose, respectively. Steady state concentrations are achieved within 7 days of once daily dosing. The mean accumulation ratio (Rac) was 1.7 for  $C_{max}$  and 2.4 for  $AUC_{0-24\text{ hr}}$ . Median vibegron  $T_{max}$  is approximately 1 to 3 hours.

Oral administration of vibegron 75 mg film-coated tablet crushed and mixed with 15 mL of applesauce resulted in no clinically relevant changes in vibegron pharmacokinetics when compared to administration of an intact vibegron 75 mg film-coated tablet. Therefore, vibegron can be crushed for administration in soft food.

#### *Effect of food*

Co-administration of a 75 mg tablet with a high-fat meal reduced vibegron  $C_{max}$  and AUC by 63% and 37%, respectively. The effect of food appeared to be smaller at steady state (unchanged AUC and 30% lower  $C_{max}$ ). In the phase 3 studies demonstrating efficacy and safety, vibegron was administered with or without food. Therefore, vibegron can be taken with or without food.

### Distribution

The mean apparent volume of distribution following oral administration is 9 120 litres. Human plasma protein binding of vibegron is approximately 50%. The average blood-to-plasma concentration ratio is 0.9.

### Biotransformation

Vibegron is metabolised via oxidation and direct glucuronidation but metabolism is not a major route of elimination. Vibegron is the major circulating component following a single dose of <sup>14</sup>C-vibegron. One major metabolite was observed in human plasma being a phase II glucuronide representing 12 to 14% of total exposure. All the recombinant UGT enzymes evaluated *in vitro* demonstrated some metabolism of vibegron (mainly UGT1A3, UGT1A4, UGT1A6, UGT2B10, UGT2B15). Although *in vitro* studies suggest a role for CYP3A4 in the oxidative metabolism of vibegron, *in vivo* results indicate that these isozymes play a limited role in the overall elimination.

### Elimination

The mean terminal half-life ( $t_{1/2}$ ) values following multiple-dose administration ranges from 59 to 94 hours in young and elderly subjects, and the effective half-life is approximately 31 hours across all populations.

Following the oral administration of 100 mg <sup>14</sup>C-vibegron to healthy volunteers, approximately 59% of the radiolabeled dose was recovered in faeces and 20% in urine. Unchanged vibegron accounted for the majority of the excreted radioactivity (54 and 19% of the radiolabelled in faeces and urine, respectively). Most of the dose recovered in faeces is likely unabsorbed substance. Urinary excretion of unchanged substance is a major route of elimination (around 50% of the absorbed vibegron). Biliary excretion of unchanged substance may also contribute to the elimination while hepatic metabolism appears to play a minor part.

### Renal impairment

Relative to volunteers with normal renal function ( $\text{GFR} \geq 90 \text{ mL/min}$ ), administration of 100 mg single dose of vibegron increased mean  $C_{\text{max}}$  and AUC by:

- 1.6- and 2.1-fold, respectively in volunteers with mild renal impairment ( $60 \leq \text{GFR} < 90 \text{ mL/min}$ )
- 2.0- and 1.6-fold, respectively in volunteers with moderate renal impairment ( $30 \leq \text{GFR} < 60 \text{ mL/min}$ )
- 1.8- and 1.2-fold, respectively in volunteers with severe renal impairment ( $\text{GFR} < 30 \text{ mL/min}$ )

No dose adjustment for vibegron is recommended for patients with mild, moderate, or severe renal impairment ( $15 \text{ mL/min} < \text{GFR} < 90 \text{ mL/min}$  and not requiring dialysis). Vibegron has not been studied in patients with end stage renal disease ( $\text{GFR} < 15 \text{ mL/min}$  with or without haemodialysis) and is therefore not recommended in these patients.

### Hepatic impairment

Relative to volunteers with normal hepatic function, administration of 100 mg single dose of vibegron increased mean  $C_{max}$  and AUC by 1.3- and 1.3-fold, respectively in volunteers with moderate hepatic impairment (Child-Pugh Class B)

No dose adjustment for vibegron is recommended for patients with mild to moderate hepatic impairment (Child-Pugh A and B). Vibegron has not been studied in patients with severe hepatic impairment (Child-Pugh C) and is therefore not recommended in this patient population.

### Paediatric population

No pharmacokinetic data are available in children below 18 years of age.

### Other special populations

No clinically significant differences in the pharmacokinetics of vibegron were observed based on age (studied range: 18 to 93 years), gender or race/ethnicity.

Weight (studied range: 39 to 161 kg) had a modest effect on clearance and central volume of distribution in the population pharmacokinetic analysis. The increase in vibegron exposures resulting from differences in weight are not considered clinically significant.

## **5.3 Preclinical safety data**

Vibegron showed 9 and 78-times lower *in vitro*  $\beta$ 3-AR potency for rabbits and rats, respectively, when compared to humans. Therefore, safety margins for potential  $\beta$ 3-AR-mediated effects on development or reproduction are accordingly lower than for non- $\beta$ 3-AR-related effects.

In animal studies no effects on embryo-foetal development were observed following oral administration of vibegron during the period of organogenesis at exposures (AUC) approximately 275-fold and 285-fold greater than clinical exposure at the recommended human dose (RHD) of 75 mg/day vibegron, in rats and rabbits, respectively. Delayed foetal skeletal ossification and reduced foetal body weights were observed in rabbits at approximately 898-fold clinical exposure (AUC) at the RHD, in the presence of maternal toxicity. In rats treated with vibegron during pregnancy and lactation, no effects on offspring were observed at 89-fold clinical exposure at the RHD. Developmental toxicity was observed in offspring at approximately 458-fold clinical exposure (AUC) at the RHD, in the presence of maternal toxicity.

When a single oral dose of radiolabeled vibegron was administered to postnatal nursing rats, radioactivity was observed in milk.

No effects on fertility were observed in female or male rats at doses up to 300 mg/kg/day, associated with systemic exposure (AUC) at least 275-fold higher than in humans at the RHD of 75 mg/day. General toxicity, decreased fecundity, and decreased fertility were observed in female rats at 1 000 mg/kg/day, associated with estimated systemic exposure 1 867-fold higher (AUC) than in humans at the RHD of 75 mg/day.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Core tablet

Mannitol  
Microcrystalline cellulose  
Croscarmellose sodium  
Hydroxypropylcellulose  
Magnesium stearate

#### Film coating

Indigo carmine aluminium lake (E132)  
Hypromellose (E464)  
Iron oxide yellow (E172)  
Lactose monohydrate  
Titanium dioxide (E171)  
Triacetin

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

5 years.

#### **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

#### **6.5 Nature and contents of container**

HDPE white, square or round bottle respectively closed with a child resistant polypropylene (PP) cap and an inner seal containing a polyethylene (PE) layer in contact with the tablets. Each bottle contains 7, 30 or 90 film-coated tablets.

Not all pack sizes may be marketed.

#### **6.6 Special precautions for disposal**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

### **7 MARKETING AUTHORISATION HOLDER**

PIERRE FABRE LIMITED  
250 Longwater Avenue,  
Green Park,  
Reading. RG2 6GP  
United Kingdom

### **8 MARKETING AUTHORISATION NUMBER(S)**

PLGB 00603/0250

### **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

17/07/2024

**10 DATE OF REVISION OF THE TEXT**

06/03/2025