Obgemsa (Vibegron)
75 mg
Film-coated tablet

RISK MANAGEMENT SYSTEM

Section 1.8.2.

EU Risk Management Plan for Obgemsa (Vibegron)

RMP version to be assessed as part of this application:

- RMP Version number: Version 0.4
- Data lock point for this RMP: 20 September 2022
- Date of final sign-off: 03 June 2024
- Rationale for submitting an updated RMP: Not applicable; Initial RMP
- Summary of significant changes in this RMP: Not applicable; Initial RMP

Qualified Person Responsible for Pharmacovigilance (QPPV)

EU QPPV name: Isabelle GEORGE

EU QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant´s EU QPPV. The electronic signature is available on file.

Table of Contents

List of Tables

List of Abbreviations

ADD	Average daily dose
ADR	Adverse drug reaction
AEs	Adverse events
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the concentration-time curve
$AUC_{0-\infty}$	Area under the concentration-time curve from time 0 extrapolated to infinity
β_x-AR	Beta-x adrenergic receptor
BPH	Benign prostatic hyperplasia
CI	Confidence interval
C_{max}	Maximal concentration
CNS	Central nervous system
CVA	Cerebrovascular accident
CYP	Cytochrome P450
DBP	Diastolic blood pressure
ECG	Electrocardiogram
EEA	European Economic Area
EFD	Embryo-foetal development
eGFR	Estimated glomerular filtration rate
EPAR	European public assessment report
ER	Extended release
EU	European Union
GD	Gestational day
GMR	Geometric mean ratio
HR	Heart rate
IBD	International Birthdate
IBS	Irritable bowel syndrome
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INN	International Non proprietary Name

IV	Intravenous
LOAEL	Low Observable Adverse Effect Level
MAA	Marketing Authorisation Application
MACCE	Major adverse cardiac and cerebrovascular event
MDRD	Modification of diet in renal disease
NC	Not calculated
NHPs	Non-Human Primates
NOAEL	No-observed-adverse-effect level
OAB	Overactive bladder
P-gp	P-glycoprotein
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic(s)
PL	Package leaflet
PND	Post-natal day
POP	Pelvic organ prolapse
PPND	Pre-/post-natal development
PSUR	Periodic safety update report
PTD	Patient treatment days
PTY	Patient treatment years
QPPV	Qualified person for pharmacovigilance
RMP	Risk Management Plan
SAE	Serious adverse event
SBP	Systolic blood pressure
SmPC	Summary of Product Characteristics
TQT	Thorough QT
TTC	Threshold of toxicological concern
UGT	Uridine Diphosphate Glucuronosyltransferase
ULN	Upper limit of normal
Urovant	Urovant Sciences GmbH
US	United States
UVR	Ultraviolet radiation

Part I: Product overview

An overview of Obgemsa (Vibegron) is provided in Table 1.

Table 1: Product Overview

Active substance (INN or common name)	Vibegron
Pharmacotherapeutic group (ATC Code)	Urologicals, urinary antispasmodics (ATC: G04BD15)
Marketing Authorisation Applicant	Pierre Fabre Médicament
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Obgemsa
Marketing authorisation procedure	Centralised procedure
Brief description of the product	Chemical class: pyrrolopyrimidines
	Summary of mode of action: Vibegron is a selective and potent human beta-3 adrenergic receptor (β3-AR) agonist over β1-AR and β2-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.
	Important information about its composition: Excipient with known effect: Each film-coated tablet contains 1.6 mg of lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
Hyperlink to the Product Information	See the proposed Product Information (Module 1.3.1).
Indication in the EEA	Vibegron is indicated in symptomatic treatment of overactive bladder (OAB) syndrome in adult patients.
Dosage in the EEA	The recommended dose is 75 mg once daily.
Pharmaceutical form(s) and strengths	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) × 3 mm (height). Each film-coated tablet contains 75 mg of vibegron.

Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

This Risk Management Plan (RMP) supports an initial Marketing Authorisation Application (MAA) and contains all completed sections.

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Indication: Treatment of overactive bladder (OAB) syndrome symptoms in adults

Incidence/prevalence

The incidence and prevalence of OAB in adults are difficult to estimate for several reasons. Many OAB patients may not seek medical care due to the negative social impact OAB symptoms may have on social and medical well-being. It is estimated that about 10% of the adult population have lower urinary tract symptoms and OAB across Canada, Germany, Italy, Sweden, and the United Kingdom [EPIC Study; [Irwin, 2006]. Similarly, another study conducted in the United States (US) (NOBLE Study) found a prevalence of about 16% for OAB [Stewart, 2003]. Only 16% to 23% of patients with OAB symptoms seek professional help, and of them, only about half are treated with a pharmacological agent [Milsom, 2001]. Also, accurate epidemiologic incidence and prevalence studies for OAB may have been hampered in the past by a generalised lack of agreement regarding definition of the disorder, and consequently, accurate case finding [Rovner, 2002].

A review analysing 5 key studies on the epidemiology of OAB in several countries across Europe, the US and Canada showed that the prevalence in adults ranged from 11.8% to 35.6% in the European Union (EU) and US [Eapen, 2016] and reached 16.6% in Europe specifically [Milsom, 2001].

Demographics of the population in the proposed indication and risk factors for OAB

OAB is a clinical syndrome characterised by urinary urgency (i.e., a sudden compelling desire to void that is difficult to defer), with or without urge incontinence, and usually accompanied by urinary frequency and nocturia [Scarneciu, 2021; Stewart, 2003; Abrams, 2002; Milsom, 2001; Austin, 2016]. Although its aetiology is not completely clear, it involves detrusor overactivity, which may have a neurogenic and non-neurogenic origin (i.e., idiopathic) [Austin, 2016].

In a population-based survey, the overall prevalence of OAB in Europe has been estimated to be 16.6%, with a slightly higher prevalence in women than in men (17.4% vs. 15.6%, respectively). The overall prevalence of frequency and urgency was comparable irrespective of gender. However, urge incontinence was found to be more prevalent among women than men [Milsom, 2001].

For both genders, the prevalence of OAB significantly increases with age. OAB affects approximately one third of adults over 75 years of age [Sexton, 2009; Stewart, 2003; Milsom, 2001]. In addition, obesity also relates with an increase in the prevalence of OAB [Lai, 2019].

Main existing treatment options

There are a number of non-pharmacologic and pharmacologic therapeutic options available for patients with OAB. Non-pharmacologic and first-line treatments include lifestyle changes (e.g., weight loss, controlled fluid intake), behavioural therapies, physiotherapy, pelvic floor electrical stimulation, neuromodulation, and surgical procedures, whereas the pharmacologic options indicated in the treatment of OAB aim at reducing or suppressing the intensity of involuntary detrusor contractions.

Currently, the predominant class of drugs prescribed in the treatment of OAB is still from the antimuscarinics (e.g., tolterodine, oxybutynin, trospium, propiverine, solifenacin, darifenacin,

fesoterodine). They are often associated with tolerability issues due to mechanism-based side effects including dry mouth and constitutional effects (constipation/gastrointestinal effects) [Harding, 2022; Leron, 2018]. In addition, there is increasing evidence that these drugs are associated with cognitive impairment and a risk of dementia. Due to the tolerability issues with antimuscarinics, patient adherence and persistence of chronic administration with prescribed therapies remain a significant barrier to effectiveness. In a survey of 6,577 users of OAB medications, Benner et al found that of the 25% respondents who had discontinued an antimuscarinic in the previous 12 months, the primary reason reported for discontinuation was unmet treatment expectations (46%) or tolerability issues (21%) [Benner, 2010]. In addition, anticholinergics can cross the blood-brain barrier and may cause central nervous system (CNS) effects. Several reports show that the long-term use of antimuscarinics and other anticholinergic agents is associated with increased risks of cognitive impairment and dementia [Campbell, 2019; Coupland, 2019; Risacher, 2016; Gray, 2015; Welk, 2020; Zillioux, 2022]. These cognitive deficits can be especially detrimental in the elderly.

A first β_3-AR agonist (mirabegron) has been approved in 2012 for the symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with OAB syndrome [Betmiga EPAR/Product Information, 2021]. Mirabegron activates the β_3-AR subtype, which is the most prevalent β-AR subtype expressed on human detrusor smooth muscle, leading to muscle relaxation and an increase in bladder capacity [Takeda, 2002; Nitti, 2013]. Mirabegron has shown comparable efficacy to antimuscarinics but has had fewer dose-limiting side effects. The most frequently reported adverse reactions are hypertension, nasopharyngitis, urinary tract infection, and headache. In addition, mirabegron is a cytochrome P450 (CYP)2D6 inhibitor and has been associated with QT interval (QT) prolongation at supratherapeutic doses. Because it is an extended-release product, it cannot be crushed for administration.

Other therapies include minimally invasive procedures to treat OAB, such as injections of onabotulinum toxin A into the detrusor muscle via cystoscopy, posterior tibial nerve stimulation and more invasive procedures including surgically implanted neuromodulation devices and urinary diversion. These all require anaesthesia.

Natural history of overactive bladder in the untreated population, including mortality and morbidity

Although OAB is not life threatening, the consequences of untreated OAB are broad and include an adverse impact to health-related quality of life as well as direct medical effects [Reynolds, 2016].

The condition can be highly disruptive and distressing and significantly impact normal daily functions and sleep. Patients consider urinary leakage, frequency, and urgency to be bothersome. Consequent sleep disturbances, restricted mobility, isolation, and depression are all described as the psychological and lifestyle-related consequences of OAB. Many OAB sufferers report detriments to psychological well-being (self-esteem, sexuality, personal relationships), social engagement, work productivity, and physical activity, all of which can have potentially significant health consequences [Coyne, 2013].

Direct medical effects and complications include urinary tract infection, skin ulceration in OAB with urge incontinence, and a greater risk of fall and bone fractures in some reports.

Important co-morbidities

Important co-morbidities that occur frequently in patients with OAB include [Rutman, 2021; Coyne, 2013; Lai, 2019]:

- Cardiovascular diseases, in particular hypertension;
- Depression/anxiety;
- Dementia;
- Obesity;
- Diabetes mellitus.

Part II: Module SII - Non-clinical part of the safety specification

The key safety findings from non-clinical studies and their relevance to safety in humans are summarised hereafter.

Toxicity

- Key issues identified from acute or repeat-dose toxicity studies

Vibegron showed 9 and 78-times lower in vitro β3-AR potency for rabbits and rats, respectively, when compared to humans. Therefore, safety margins for potential β3-AR-mediated effects are accordingly lower than for non-β3-AR-related effects. However, low safety margins in rat studies have little relevance for humans given that the pharmacological effect is more profound in rat compared to humans/NHPs as β3-AR expression occurs in both brown and white rat adipose tissue while in humans/NHPs it occurs mainly in brown adipose tissue.

In CD-1 mice, unscheduled deaths occurred at doses of ≥250 mg/kg/day in males and ≥500 mg/kg/day in females, which corresponded to a C_{max} at least 266-fold and an AUC at least 106-fold of the clinical exposure at 75 mg/day.

In rats, oral vibegron doses of ≥750 mg/kg/day were associated with clinical signs of toxicity (including gasping and sternal recumbency). At 750 mg/kg/day, the associated C_{max} was 680-fold, and the associated AUC was 600-fold higher than the clinical exposure at 75 mg/day.

In monkeys, at doses of 1,000 mg/kg/day, deaths of 2 females occurred (Week 3) following signs of toxicity (including decreased activity and/or coldness to the touch). Based on ECG changes in surviving animals at this dose, these sudden deaths may have been the consequence of severe cardiac arrhythmias. The systemic exposure at Week 3/4 (closest time point to the deaths) for 1,000 mg/kg/day corresponded to a C_{max} of 180-fold and an AUC of 255-fold the human exposure at 75 mg/day (1,000 mg/kg/day proved toxic and was reduced at Week 3 to 360 mg/kg/day), indicating high safety margins.

The review of the repeat-dose toxicity data found some signs of cardiovascular effects. Increased QRS duration at very high multiples of clinical exposure and no HR increase (exposure margin from the 9 month toxicity study in monkey was 34fold [for C_{max}] and 17-fold [for AUC]); No important safety concerns are identified. Additionally, the cardiovascular-related effects were thoroughly assessed during clinical development of vibegron with no adverse reactions suggestive of cardiovascular concerns.

Hepatic effects such as slightly elevated hepatic enzyme levels (in rats at 180 mg/kg/day and monkeys at ≥300 mg/kg/day) and slight cellular infiltration in the liver (at ≥300 mg/kg/day in monkeys) were observed. In general, hepatic findings across toxicology studies were only observed at exposures much

higher (≥72-fold) than clinical exposure at 75 mg/kg. The potential increase in hepatic enzymes was carefully assessed during the clinical development of vibegron and no important safety concern was identified.

- Reproductive/developmental toxicity

No effects on fertility were noted in female and male rats at doses up to the maximum dose tested of 300 mg/kg/day, associated with systemic exposure (AUC) at least 274-fold higher than the clinical exposure at 75 mg/day. Reduced fertility was observed in female rats at 1,000 mg/kg/day, a dose that was associated with mortality. No effects on fertility potential in humans were identified based on non-clinical findings.

The embryo-foetal NOAELs in rats and rabbits were 300 and 100 mg/kg/day, respectively, which were equivalent to approximately 275- and 285-fold higher than human exposure at the clinical dose of 75 mg/day.

In rats, there was no evidence of developmental toxicity in the 30-, 100-, or 300-mg/kg/day groups. However, the safety margin for embryo-foetal toxicity based on the rat teratology study may be 78-times lower due to the lower potency of vibegron to the β3-AR for rats when compared to humans. Consequently, an embryo-foetal toxicity in human cannot be totally excluded and teratogenicity should be considered as a safety concern in humans.

In rabbits, there was no evidence of developmental toxicity in the 30-mg/kg/day or 100-mg/kg/day groups. However, in the 300-mg/kg/day group, there was a vibegron-related decrease in mean live foetal weight (14% and 9% below the control group in female and male foetuses, respectively) which was associated with a slightly increased incidence of foetuses with sites of incompletion ossification (i.e., incomplete ossification of the skull bone, sternebra, metacarpal, and talus-calcaneus).

In a rabbit EFD study, delayed skeletal ossification occurred at 300 mg/kg/day, which corresponded to exposures approximately 898-fold higher than the clinical exposure at 75 mg/day. The safety margin for embryo-foetal toxicity based on the rabbit teratology study may be 9-times lower due to the lower potency of vibegron to the β3-AR for rabbits when compared to humans. Consequently, an embryo-foetal toxicity in human cannot be totally excluded and teratogenicity should be considered as a safety concern in humans.

In a PPND study in rats, vibegron caused developmental impacts on F1 offspring (including increased stillborn and low viability indices) at 500 mg/kg/day, which corresponds to approximately 458-fold clinical exposure, in the presence of maternal toxicity (decreased body weight gain and food consumption). The NOAEL for reproductive and developmental toxicity of 100 mg/kg/day, corresponded to an exposure approximately 90-fold higher than that at the clinical dose of 75 mg/day. Non-clinical findings do not suggest a specific risk for clinical use.

- Genotoxicity

Vibegron was not genotoxic in a standard core battery of in vitro and in vivo studies that included microbial mutagenesis, chromosomal aberration, and rat micronucleus assays.

In the vibegron drug substance, there are no impurities of mutagenic potential at a level that would exceed the TTC as defined by the ICH M7 guidance on the limits of genotoxic impurities.

- Carcinogenicity

No evidence of a carcinogenic potential was observed in two 2-year oral carcinogenicity studies conducted in mice and rats.

Safety Pharmacology

Reversible neuro-behavioural changes were observed, such as decreased locomotion and abnormal posture and gait (exposure margin from the single dose study in rats was 33-fold); No important safety concerns are identified.

No effect on intestinal charcoal transit rate (exposure margin from a gastrointestinal safety study in rats was 170-fold).

Other toxicity-related information or data

- Absorption, tissue distribution, metabolism, and excretion

PK of vibegron after IV and oral dosing have been evaluated in multiple animal species. Oral bioavailability was moderate (around or below 50%) and data from mice suggested a role of P-gp in drug transport.

In a whole-body autoradiography study in rats, orally administered radiolabelled vibegron was rapidly distributed into most tissues, except the lens of the eye and the non-circumventricular CNS tissues that were devoid of radioactivity, indicating that vibegron and its metabolites did not penetrate the blood-brain barrier at detectable levels. Slowly declining levels of radioactivity were also observed in pigmented ocular tissues, suggesting a potential affinity for melanin; however, this increased affinity was not confirmed since not detected in other tissues having an increased melanin content, including skin and hair follicles. In a placental transfer study in rats, the distribution of vibegron and its metabolites to the foetus was low.

In rats, the urinary and biliary excretion of unchanged vibegron are the major routes of excretion, and the enterohepatic recirculation of vibegron-derived components is suggested as a potential route. In human, vibegron is eliminated by a variety of pathways, including urinary excretion, biliary excretion, and hepatic metabolism. Vibegron is a CYP3A4 and UGT substrate.

In rats, vibegron-derived material was excreted into dams' milk with a maximum milk to plasma concentration ratio of 2.2 following oral dose administration. Vibegron is excreted in the milk of rodents; it is therefore predicted to be present in human milk.

- Juvenile Toxicity

No new vibegron-related toxicities were identified in juvenile rats dosed from PND 23 through to PND 114. Findings were largely consistent with established data in adult animals and likely related to the β3-adrenergic agonistic effect of vibegron (decreases in body weight in males and increases in brown fat in both sexes). These changes are reversible.

- Phototoxicity

Vibegron was not phototoxic in Long-Evans (pigmented) rats at doses up to 300 mg/kg/day for 3 days followed by exposure to UVR. In a placental transfer study conducted in pregnant rats, the distribution of vibegron across the placenta was limited. The human foetus exposure to vibegron via placental circulation is unknown (see reproductive toxicity section below).

Conclusion:

The potential safety concern in humans identified based on non-clinical findings, is summarised in Table 2.

Table 2: Conclusion on Safety Concerns from Non-clinical Part

Summary of safety concerns	
Important identified risks	None
Important potential risks	Embryo-foetal toxicity
Missing information	None

Part II: Module SIII - Clinical trial exposure

The overall clinical development programme of vibegron consists of:

- Phase 1 studies:
    - 21 completed Phase 1 studies conducted in healthy adults;
    - 1 completed Phase 1 study conducted in patients with OAB (study 1001), in addition to another Phase 1 study in female patients with OAB which was early terminated due to difficult recruitment (study 004);
- Phase 2 and 3 studies in patients with OAB:
    - 1 completed International Phase 2b study (Study 008), which included study sites in the EU, Australia, Japan and the US;
    - 2 completed Phase 3 studies (Studies 301 and 302) conducted in Japan,
    - 2 completed Phase 3 studies (Studies 3003 and 3004) conducted in North America and Europe;
    - 1 ongoing Phase 3 study (study JLP-2002-301) conducted in Korea
- Other Phase 2 and 3 studies:
    - For Irritable Bowel Syndrome in adults: 1 completed Phase 2 study in the US (Study 2001);
    - For OAB in men with BPH: 2 ongoing Phase 3 studies in North America and Europe (Study 3005 [double-blind study] and Study 3006 [open-label extension]).

In addition to the Phase 3 pivotal studies (Studies 3003 and 3004) and the dedicated ambulatory blood pressure study in patients with OAB (Study 1001), clinical safety data focus was on:

- Pool 1: treatment data from the 2 double-blind, placebo-controlled, 12-week studies of vibegron (Study 301 and Study 3003).
- Pool 3: long-term data (Studies 008 Part 1 and its extension combined, Study 008 Part 2 and its extension combined, Study 302, and Study 3003/3004 combined) to evaluate the safety of vibegron with long-term exposure (up to 12 months).

A total of 643 healthy subjects participating in 21 Phase 1 clinical studies received vibegron at single doses ranging from 2 to 600 mg, multiple once-daily doses ranging from 25 to 400 mg for 14 days, or once-daily doses of 150 mg for 28 days.

A total of 2625 patients with OAB received vibegron in the Phase 1 Study 1001, the Phase 2b Study 008, and the Phase 3 Studies 301, 302, 3003, and 3004 as either monotherapy or in combination with tolterodine.

The exposure to vibegron during the clinical development for all indications and for OAB in particular is provided by cumulative subject exposure (Table 3), duration of exposure (Table 4), gender (Table 5), age group (Table 6), dose level (Table 7) and racial group (Table 8).

Table 3: Estimated Cumulative Subject Exposure from Ongoing and Completed Clinical Studies

Treatment	Number of Subjects/Patients
Cumulative for clinical pharmacology studies[a]	
Vibegron	643
Placebo	55
Total	**698**
Cumulative for all indications[b]	
Vibegron	3156
Placebo	1835
Comparator	974
Total	**5965**
Cumulative for OAB[c]	
Vibegron	2625
Placebo	1222
Comparator	974
Total	**4821**

OAB = Overactive bladder.
[a] Data from the 22 ongoing and completed clinical studies were included (excluding study 901-1001).
[b] Data from 9 ongoing and completed studies: 301, 302, 008, 901-3003, 901-3004, 901-1001, 901-3005, 901-3006, 901-2001, excludes combination therapy. Estimated number of subjects are used for the ongoing studies: Studies 901-3005 and 3006.
[c] Data from 6 completed studies (Studies 301, 302, 008, 3003, 3004, 1001), includes combination therapy.

Table 4: Cumulative Subject Exposure to Vibegron from Completed Studies by Duration of Exposure

Treatment	Number of Subjects/Patients	Person Time (Years)
Cumulative for all indications [a]		
<4 weeks	63	1.8
≥4 weeks to <12 weeks	809	138
≥12 weeks to <24 weeks	830	200
≥24 weeks to <48 weeks	146	105
≥48 weeks	669	712
Total	**2517**	**1155**
Cumulative for OAB [b]		
<4 weeks	68	2.1
≥4 weeks to <12 weeks	858	143
≥12 weeks to <24 weeks	764	186
≥24 weeks to <48 weeks	154	110
≥48 weeks	781	838
Total	**2625**	**1278**

OAB = Overactive bladder.
[a] Including data from 7 completed studies (Studies 301, 302, 008, 3003, 3004, 1001, 2001) and excluding combination therapy.
[b] Including data from 6 completed studies (Studies 301, 302, 008, 3003, 3004, 1001) and including combination therapy.
Note: For the 2-part (base and extension) Study 008, if the patient received vibegron containing treatment in the base study (part 1 or 2) and continued in the extension study, exposure is evaluated from the start of the base study.

Table 5: Cumulative Subject Exposure to Vibegron from Completed Clinical Studies by Gender

Treatment	Number of Subjects/Patients	Person Time (Years)
Cumulative for clinical pharmacology studies[a]		
Male	461	NC
Female	182	NC
Total	**643**	**NC**
Cumulative for all indications[b]		
Male	295	145
Female	2222	1011
Total	**2517**	**1155**
Cumulative for OAB[c]		
Male	323	163
Female	2302	1116
Total	**2625**	**1278**

NC= Not calculated; OAB = Overactive bladder.
[a] Including data from the 22 completed clinical studies (excluding Study 1001, which enrolled patients diagnosed with OAB).
[b] Including data from 7 completed studies (Studies 301, 302, 008, 3003, 3004, 1001, 2001) and excluding combination therapy.
[c] Including data from 6 completed studies (Studies 301, 302, 008, 3003, 3004, 1001) and including combination therapy.

Table 6: Cumulative Subject Exposure to Vibegron from Completed Clinical Studies by Age Group

Treatment	Number of Subjects/Patients	Person Time (Years)
Cumulative for clinical pharmacology studies[a]		
≥18 years to <65 years	570	NC
≥65 years to <75 years	66	NC
≥75 years to <85 years	7	NC
≥85 years	0	NC
Total	**643**	**NC**
Cumulative for all indications[b]		
≥18 years to <65 years	1631	733
≥65 years to <75 years	715	348
≥75 years to <85 years	162	71
≥85 years	9	4.6
Total	**2517**	**1155**
Cumulative for OAB [c]		
≥18 years to <65 years	1689	823
≥65 years to <75 years	762	378
≥75 years to <85 years	165	73
≥85 years	9	4.6
Total	**2625**	**1278**

NC= Not calculated; OAB = Overactive bladder.
[a] Including data from the 22 completed clinical studies (excluding Study 1001, which enrolled patients diagnosed with OAB). Person time is not calculated for the clinical pharmacology studies.
[b] Including data from 7 completed studies (Studies 301, 302, 008, 3003, 3004, 1001, 2001) and excluding combination therapy.
[c] Including data from 6 completed studies (Studies 301, 302, 008, 3003, 3004, 1001) and including combination therapy.

Table 7: Cumulative Subject Exposure to Vibegron from Completed Studies by Dose Level

Treatment	Number of Subjects/Patients	Person Time (Years)
Cumulative for all indications [a]		
<50 mg	278	173
50 mg	829	447
75 mg	854	345
100 mg	756	361
Total	**2717**	**1327**
Cumulative for OAB[b]		
<50 mg	278	173
50 mg	893	468
75 mg	743	321
100 mg	911	488
Total	**2825**	**1449**

OAB = Overactive bladder.
[a] Including data from 7 completed studies (Studies 301, 302, 008, 3003, 3004, 1001, 2001) and excluding combination therapy.
[b] Including data from 6 completed studies (Studies 301, 302, 008, 3003, 3004, 1001) and including combination therapy.
Note: For the 2-part (base and extension) of Study 008, if the patient received vibegron containing treatment in the base study (part 1 or 2) and continued in the extension study, exposure is evaluated from the start of the base study.

Table 8: Cumulative Subject Exposure to Vibegron from Completed Studies by Racial Group

Treatment	Number of Subjects/Patients
Cumulative for all indications[a]	
Asian	1096
Black	170
Caucasian	1224
Other	27
Unknown	0
Total	**2517**
Cumulative for OAB[b]	
Asian	1170
Black	156
Caucasian	1267
Other	32
Unknown	0
Total	**2625**

OAB = Overactive bladder.
[a] Including data from 7 completed studies (Studies 301, 302, 008, 3003, 3004, 1001, 2001) and excluding combination therapy.
[b] Including data from 6 completed studies (Studies 301, 302, 008, 3003, 3004, 1001) and including combination therapy.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1. Exclusion criteria in pivotal clinical studies within the development programme

The important exclusion criteria in the pivotal Phase 3 clinical Studies 3003 and 3004 across the development programme for the treatment of OAB are listed in Table 9.

Table 9: Important Exclusion Criteria from the Pivotal Studies 3003 and 3004

Criterion	Reason for exclusion	Included as missing information (Yes/No)	Rationale for not including as missing information (if applicable)
Age group			
Paediatric patients <18 years	Clinical development programmes usually investigate first the benefit/risk in adults.	No	Paediatric population is not part of the current indication. Of note, a positive opinion was obtained in June 2022 for a PIP for treatment of detrusor overactivity in children with neurogenic bladder disfunction (EMEA-001415-PIP02-21).
Urology medical history			
Lower urinary tract pathology that could, in the opinion of the investigator, be responsible for urgency, frequency or incontinence	Allowance of this condition would confound assessment of safety and efficacy.	No	The assessment of an OAB patient should include an evaluation of the symptoms that are due to another underlying disease.
History of surgery to correct stress urinary incontinence, POP, or procedural treatments for BPH within 6 months of screening	Allowance of this condition would confound assessment of safety and efficacy.	No	OAB patients would be assessed if their symptoms and urinary incontinence are predominantly due to OAB.
Other medical history			
Evidence of diabetes insipidus	Allowance of this condition would confound assessment of efficacy.	No	Diabetes insipidus may lead to polyuria and not OAB, which will confound the efficacy assessments.

Criterion	Reason for exclusion	Included as missing information (Yes/No)	Rationale for not including as missing information (if applicable)
Pregnant, breastfeeding or planning to conceive	Clinical development programmes do not initially investigate benefit/risk in pregnant, breastfeeding or planning to conceive women.	No	Vibegron is not recommended during pregnancy and in women of childbearing potential not using contraception, as per the prescribing information. In addition, a recommendation is included in the prescribing information to stop treatment with vibegron when pregnancy is planned or diagnosed. Vibegron should not be used during breast-feeding, as per the prescribing information.
Signs and symptoms of uncontrolled hypertension	Allowance of this condition would confound assessment of safety and efficacy.	No	No cardiovascular concerns were observed following thorough cardiovascular-related risks assessment.
Known history of liver disease	Vibegron is eliminated by a variety of pathways, include biliary excretion, renal excretion, and hepatic metabolism. Allowance of this condition might expose the patient at risk and could potentially lead to elevated drug exposures. Pre-existing liver disease may confound assessment of safety	No	The use of vibegron in patients with hepatic impairment is well addressed in the prescribing information. In addition, the use of vibegron in patients with severe hepatic impairment is not recommended.
History of injury, surgery or neurodegenerative diseases that could affect the lower urinary tract or its nerve supply	Allowance of this condition would confound assessment of efficacy.	No	These conditions would need to be evaluated for appropriate patient selection first, before prescribing an OAB medication.
Allergy, intolerance, or a history of a significant clinical or laboratory adverse experience associated with vibegron or inactive components of the formulation	Patients with a medical history of significant allergic reactions following the administration of vibegron or the excipients are at increased risk for hypersensitivity reactions.	No	A contraindication to not administer a drug to patients with known allergic reactions to any specific active substance or excipients has been added.

Criterion	Reason for exclusion	Included as missing information (Yes/No)	Rationale for not including as missing information (if applicable)
Clinically significant ECG abnormality that exposes the patient at risk	Allowance of this condition would expose the patient to cardiac safety risks.	No	No evidence of ECG findings such as QT prolongation or arrhythmias in clinical studies.
Renal impairment: eGFR <30 mL/min/1.73 m^{2}[a]	Vibegron is eliminated by a variety of pathways, including urinary excretion. Allowance of this condition might expose the patient at risk and could potentially lead to elevated drug exposures.	No	The use of vibegron in patients with renal impairment is well addressed in the prescribing information. In addition, the use of vibegron with end-stage renal disease is not recommended, as per the prescribing information.

BPH = Benign prostatic hyperplasia; ECG = Electrocardiogram; eGFR = Estimated glomerular filtration rate; OAB = Overactive bladder; PIP = Paediatric investigation plan; POP = Pelvic organ prolapse.
[a] Of note, patients with severe renal impairment (i.e., 15<eGFR<30 mL/min/1.73 m^2) were not included in the clinical studies because of the high potential for changes in drug exposure.

SIV.2. Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3. Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 10: Exposure of Special Populations included or not in the OAB clinical trial development programme

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme. Three pregnancies were reported in patients in the clinical development of vibegron.
Breastfeeding women	Not included in the clinical development programme
Patients with relevant co-morbidities:	
Patients with hepatic impairment	Number of patients with OAB with hepatic impairment (ALT or AST > 2 x ULN or bilirubin > 1.5 x ULN): 8 (0.3%) patients
Patients with renal impairment[b]	Number of patients with OAB[a] with severe renal impairment (i.e., 15<eGFR<30 mL/min/1.73 m^2)[b]: 0[c]
Patients with cardiovascular impairment	Number of patients with OAB with SBP≥160 mmHg with stable hypertension medication: 7 (0.27%) patients
Immunocompromised patients	Not included in the clinical development programme
Patients with a disease severity different from inclusion criteria in clinical studies	Not included in the clinical development programme
Population with relevant different ethnic origins	Several racial groups were studied, and none were particularly under-represented (see Table 8)
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development programme
Paediatric patients	Patients <18 years were not included in the clinical development programme
Elderly (≥65 years old)	Several age groups are presented in Table 6, including patients aged ≥85 years: 9 (0.36%) patients

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; eGFR = Estimated glomerular filtration rate; MDRD = Modification of diet in renal disease; OAB = Overactive bladder; SBP = Systolic blood pressure; ULN = Upper limit of normal.
[a] Including only patients receiving vibegron at 75 or 100 mg in Studies 008 (base), 301, 3003 and 1001.
[b] eGFR is estimated using the MDRD equation.
[c] Of note, patients with severe renal impairment (i.e., 15<eGFR<30 mL/min/1.73 m²) were not included in the clinical studies because of the high potential for changes in drug exposure.

Part II: Module SV - Post-authorisation experience

SV.1. Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Vibegron has been approved in Japan for the treatment of adults with OAB since 21 September 2018 (International Birthdate [IBD]). Patient exposure to vibegron is derived from the post-authorisation experience following the approval of Beova® in Japan in September 2018 and of Gemtesa® in the US on 23 December 2020 for the treatment of OAB at respective oral doses of 50 mg and 75 mg once daily.

Patient exposure to marketed Beova® and Gemtesa® was estimated as follows:

- The total number of tablets shipped was converted into a total number of milligrams (mg);
- The total number of mg was divided by the average daily dose (ADD) to estimate the number of patient treatment days (PTD). Of note, the ADD per patient is 50 mg in Japan and 75 mg in the US;
- The total number of PTD was divided by 365.25 to estimate the total number of patient treatment years (PTY).

SV.1.2 Exposure

As of 20 September 2022, the estimated cumulative exposure to vibegron for OAB (the only indication approved) is 1,054,013 PTY since the IBD.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

There is no potential for misuse for illegal purposes for vibegron based on non-clinical data. β_3-ARs are not central nervous system receptors known to mediate abuse-related effects.

Although off-label use has been reported, no significant psychiatric or euphoric effects associated with vibegron that could potentially motivate its abuse have been observed. It is very unlikely that vibegron would possess any drug abuse or dependence potential (Investigator's Brochure 2021). No signal was raised as per signal detection/routine surveillance activities.

Part II: Module SVII - Identified and potential risks

Assessment of adverse drug reactions (ADRs) through extensive review of clinical safety results identified few clinically relevant risks associated with vibegron therapy. Additionally, ADRs identified from post-marketing experience are common to OAB drugs. All the ADRs identified in clinical Studies 3003 and 3004, as well as those from spontaneous reporting are included in the Undesirable Effects Section 4.8 of the proposed vibegron EU Summary of Product Characteristics (SmPC). Studies in animals have demonstrated embryo-foetal developmental changes considered as of potential relevance for use in humans; accordingly the embryo-foetal toxicity is considered as a safety concern (important potential risk).

SVII.1. Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

The risks not considered important for inclusion in the list of safety concerns for the purpose of the RMP are the following:

- Urinary retention;
- Hypersensitivity reactions;
- Potential toxicity due to drug interaction;
- Cardiovascular-related risks;

Reasons for not including those risks in the list of safety concerns in the RMP are summarised hereafter. Monitoring of these risks is taken into consideration in all routine pharmacovigilance activities.

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)

Urinary retention

Risks related to urinary retention are due to the mechanism of action of vibegron. Indeed, vibegron is a β3-adrenoceptor agonist that exert an inhibitory effect on bladder afferent innervation through β3-adrenoceptors in the urothelium and detrusor [Yamaguchi, 2013], leading to decreased detrusor

contractility, increase bladder capacity and prolong micturition interval. Urinary retention is a risk with minimal clinical impact on OAB patients since the clinical diagnosis and management of urinary retention is a standard of care in OAB patients.

Clinical safety reports

Non-serious AEs of urinary retention (including urinary straining) have been reported in the Phase 3 clinical Studies 3003 and 3004. In the 12-week double-blind Phase 3 Study 3003, non-serious urinary retention was reported in 3 patients (0.6%) receiving vibegron 75 mg compared to 2 patients (0.4%) receiving placebo and 3 patients (0.7%) receiving tolterodine extended release (ER) 4 mg. In the long-term Phase 3 Study 3004, non-serious urinary retention was reported in 3 patients (1.1%) receiving vibegron 75 mg and 1 patient (0.4%) receiving tolterodine ER 4 mg.

Post-marketing reports

As of 20 September 2022, of the 4899 vibegron-related events reported overall in the post-marketing setting in Japan and the US, 307 events of urinary retention including the PTs urinary retention (264 events), residual urine volume increased (41 events), and urinary straining (2 events) were reported; of them, 34 events were serious and 273 were non-serious.

Overall, from all the vibegron-related events, a total of 177 serious events were reported, of which 34 serious urinary retention-related events were observed (PT: urinary retention).

Urinary retention was observed in patients taking vibegron. However, the clinical impact of urinary retention on OAB patients is considered minimal since the clinical diagnosis and management of urinary retention is a standard of care in this patient population.

In patients with higher risk for urinary retention, such as patients with bladder outlet obstruction and patients taking antimuscarinic antagonists, a warning and precaution statement is included in the product information to further remind the need to diagnose and manage urinary retention in this OAB subgroup.

***Adverse reaction**s with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated*

None.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorised)
Hypersensitivity reaction to vibegron and any of the excipients

Hypersensitivity, due to interaction of an allergen with the immune system can manifest clinically with anaphylaxis and skin disorders such as skin rash, pruritus, drug eruption, eczema and flushing of the face.

Clinical safety reports

Hypersensitivity, reported in the form of rash (including rash pruritic) and other skin reactions, was observed in patients taking vibegron. However, hypersensitivity was not determined as an ADR based on the ADR determination methodology in the safety population of clinical trials.

In the clinical studies, events of rash and eczema were observed, although all were non-serious AEs. Rash did not meet the criteria for expected ADRs in the Phase 3 Studies 3003 and 3004:

- In the 12-week double-blind Phase 3 Study 3003, non-serious rash was reported in 4 patients (0.7%) receiving 75-mg vibegron and in 4 patients (0.7%) receiving placebo;
- In the long-term Phase 3 Study 3004, non-serious rash was reported in 4 patients (1.5%) receiving 75-mg vibegron and in 2 patients (0.9%) receiving tolterodine ER 4 mg;
- The relationship of rash with the active or inactive ingredients could not be ascertained.

Post-marketing reports

As of 20 September 2022, of the 4899 vibegron-related events reported overall in the post-marketing setting in Japan and the US, 18 events suggesting hypersensitivity were reported, including the PTs: hypersensitivity (14 events), drug hypersensitivity (3 events), and anaphylactic reaction (1 event), of them 2 were serious.

Additionally, as events of rash and other skin reactions reported in post-marketing experience may represent a hypersensitivity reaction, they were also included in this section; 164 events including the PTs: rash (48 events), pruritus (43 events), erythema (25 events), drug eruption (13 events), eczema (13 events), urticaria (13 events), rash pruritic (4 events), rash erythematous (2 events), skin irritation, skin reaction and dermatitis (1 each) were reported; of them, 6 serious and 158 non-serious events.

The impact of hypersensitivity reactions is moderate and/or can be medically managed via standard of care.

This risk is already well-known to health professionals and vibegron's proposed prescribing information includes a contraindication for patients with known hypersensitivity to vibegron or any components of the drug product. Therefore, no additional pharmacovigilance activities or additional risk minimisation measures deemed necessary, and is, hence, not considered as an identified or potential risk.

Known risks that do not impact the risk-benefit profile

Potential toxicity due to drug interaction

Vibegron has been shown to be a P-gp substrate. Similarly, P-gp also includes digoxin as an important substrate [Finch, 2014], suggesting potential drug interaction between vibegron and digoxin. Interaction of vibegron with digoxin could lead to increased exposure of digoxin and potential toxicity but has not been identified as a clinical safety concern as vibegron has not been demonstrated to cause a clinically meaningful drug interaction when co-administered with digoxin.

Drug interaction studies

In the drug interaction Study 024, concomitant administration of vibegron in healthy subjects increased digoxin C_{max} and systemic exposure as measured by AUC. Multiple doses of vibegron did not cause a clinically meaningful drug interaction when co-administered with the P-gp substrate, digoxin.

Studies have been conducted to evaluate the acute-dose safety of vibegron in combination with several drugs, including digoxin: the most commonly reported AEs were headache and constipation, and there were no SAEs reported.

However, since digoxin has a quite narrow therapeutic window, this risk was considered in patients treated with digoxin for heart failure or chronic atrial fibrillation as well as elderly patients. If digoxin serum concentrations are not monitored and managed properly in patients also taking vibegron concomitantly, digoxin toxicity may occur. The impact of a concomitant use of digoxin and vibegron without titration of digoxin might result in an inappropriate dosing and clinical effect of digoxin. Caution is advised, therefore, when vibegron is

co-administered with P-gp substrates with narrow therapeutic margins (including digoxin, dabigatran etexilate, apixaban or rivaroxaban): dosing should be adjusted to the desired clinical effect by monitoring serum concentrations of P-gp substrates before, during and after cessation of vibegron treatment.

Specific recommendations have been included in the Product Information for patients treated with digoxin (see Part V.1). Drug interaction mechanisms (i.e., only with digoxin, resulting in increase in digoxin levels) and their clinical implications/management are addressed in the SmPC (section 4.5).

Recommendations about use of other sensitive P-gp substrates with narrow therapeutic margins (e.g. dabigatran etexilate, apixaban or rivaroxaban) have been also included in the Product Information (section 4.5).

The increases in digoxin AUC and C_{max} of approximately 11% and 21%, respectively, were not considered clinically meaningful since the 90% CI for the $AUC_{0-\infty}$ GMR of digoxin was contained within the 80-125% bioequivalence range. Additionally, there is no potential impact on public health because digoxin is used in a specific population and its use has declined since the 1990's [Whayne, 2018].

Other reasons for considering the risks not important

Cardiovascular-related risks

Risks related to hypertension, increased HR, major adverse cardiac and cerebrovascular events (MACCEs), and hypotension, are theoretical concerns for vibegron due to a drug of the same class that has been previously associated with increased HR in a dose dependent manner, QT prolongation at supratherapeutic doses, and has a special warning for hypertension [Betmiga® EPAR]. Cardiovascular-related risks were carefully assessed during the clinical development of vibegron and no adverse reactions suggestive of cardiovascular concerns were observed as summarised hereafter.

Blood pressure and heart rate

Isolated occurrences of orthostatic hypotension (decreased in systolic blood pressure [SBP]>20 mm Hg and/or decrease in diastolic blood pressure [DBP] >10 mm Hg) with or without symptoms, were observed in Phase 1 studies with placebo and vibegron (Module 2.7.4, Section 4.1.1.1). In the ambulatory blood pressure monitoring Study 1001, vibegron did not show statistically significant or clinically relevant effects on blood pressure or HR in patients with OAB. No clinically relevant increases in SBP, DBP and HR were observed among patients receiving 75-mg vibegron or more (Studies 3003, 3004, 301, 302, 008 [base and extension]) (Module 2.5, Section 5.4).

Electrocardiogram abnormal observations

In the thorough QT (TQT) Study 012, no clinically meaningful prolongation of the corrected QT was observed in healthy subjects receiving supratherapeutic doses of vibegron (200 mg and 400 mg associated with maximal concentration [C_{max}] values 3.3- and 9-fold higher, respectively, than the steady-state C_{max} associated with the 75 mg dose). In addition, these supratherapeutic doses of vibegron did not increase the SBP over 12 and 24 hours compared to placebo (Module 2.5, Section 5.4.4). Additionally, a pharmacokinetic/pharmacodynamic analysis further supported that 75 mg steady-state vibegron concentration is not associated with clinically meaningful changes in SBP.

In the double-blind, randomised, placebo-controlled Study 301, the incidence of treatment-emergent electrocardiogram (ECG) abnormalities was low and similar between placebo, 50-mg and 100-mg vibegron. In the long-term Study 302, clinically significant ECG findings were infrequent (≤3.5% of patients) through

52 weeks of vibegron dosing with either maintenance of initial dosage or increasing the dose from 50 mg to 100 mg (Module 2.5, Section 5.7.1).

Clinical safety reports

Hypertension or increased blood pressure are not evident from the extensive evaluations for ADRs. In the pivotal Study 3003, no difference was observed in the incidence of pre-defined AEs of hypertension (1.7% for both placebo and vibegron 75 mg) or blood pressure increase between vibegron and placebo or AEs for blood pressure increased (placebo 0.9%; vibegron 0.7%). A similar conclusion was observed for other key cardiovascular-related AEs (i.e., hypotension, dizziness, syncope, vertigo, positional vertigo, atrial fibrillation, cerebrovascular accident (CVA), chest discomfort, chest pain, sinus tachycardia). The subgroup analysis of patients with or without pre-existing or baseline hypertension showed no differences in the hypertension or blood pressure rates between treatments (Module 2.5, Section 5.3.1).

In the pivotal Studies 3003 and 3004, the only cardiovascular-related ADR was 'hot flush', observed in <2% of patients receiving vibegron 75 mg in Study 3003 (Module 2.7.4, Section 2.1.6). No cardiovascular-related AE was reported as serious or leading to treatment discontinuation in Studies 3003 and 3004 (Module 2.7.4, Section 2.1.3).

Following safety pooling of the 12-week double-blind Studies 3003 and 301, the incidence of MACCE, hypertension, and orthostatic hypotension were low across treatment groups and similar between placebo and 75-mg vibegron (Module 2.7.4, Section 2.1.4). In the vibegron 75 mg group, atrial fibrillation and cardiac failure were cardiovascular SAEs reported in 1 patient (0.2%) each (Module 2.7.4, Section 2.1.3). The only cardiovascular SAE reported in >1 patient was CVA, observed in 1 patient (0.2%) receiving vibegron 75 mg and 1 patient (0.2%) receiving tolterodine, both leading to treatment discontinuation (Module 2.7.4, Section 2.1.5).

Following safety pooling of the long-term Studies 008 (base and extension), 3004 and 302, no clinically relevant differences were observed across treatment groups for MACCE and orthostatic hypotension (Module 2.7.4, Section 2.1.4). The cardiovascular SAE reported in >1 patient overall was chest pain, observed in 1 patient (0.4%) receiving vibegron 75 mg and 1 patient (0.2%) receiving tolterodine ER 4 mg. In the vibegron 75 mg group, angina unstable, arteriosclerosis and chest pain were cardiovascular SAEs reported in 1 patient (0.4%) each (Module 2.7.4, Section 2.1.3).

Post-marketing reports

Since the approval in Japan in September 2018 and in the US in December 2020, and up to 20 September 2022, a total of 177 serious events were reported, of which the following serious cardiovascular-related events were observed: cerebral infarction (4 events), arrhythmia, bradycardia, cardiac failure, intracardiac thrombus, palpitations, ventricular tachycardia, atrial fibrillation, atrioventricular block, syncope, thalamus haemorrhage, transient ischaemic attack, implantable defibrillator insertion, circulatory collapse, deep vein thrombosis, hypotension, blood pressure abnormal, blood pressure decreased, blood pressure increased, pulmonary oedema (1 event each).

No adverse reactions suggestive of a cardiovascular risk were reported during clinical development, supporting the non-inclusion of this risk in the list. This is further supported by the limited cardiovascular-related serious events observed in the post-marketing setting of 1,054,013 PTY (see Part II: Module SV). There was no signal of cardiovascular nature indicative of an identified or potential cardiovascular risk with vibegron.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important identified risks:

There is no important identified risk for Obgemsa.

Important potential risks:

Embryo-foetal toxicity:

Studies in rabbits have demonstrated embryo-foetal developmental toxicities considered as of potential relevance for use in humans. In rats, there was no evidence of developmental toxicity. However, the safety margin for embryo-foetal toxicity based on the rat teratology study may be 78-times lower due to the lower potency of vibegron to the β3-AR for rats when compared to humans. There are no human clinical data or events reported suggesting reproductive toxicity.

Risk-Benefit Impact: The safety profile of vibegron in pregnant women and their fetuses through maternal use is not known due to the exclusion of pregnant women from the pivotal clinical studies. However, the embryo-foetal toxicity is considered an important potential risk due to the evidence resulting from the study in rabbits showing that in the 300-mg/kg/day group (approximately 898-fold greater than the clinical exposure in humans) there was a vibegron-related decrease in mean live foetal weights that was associated with a slightly increased incidence of foetuses with sites of incompletion ossification (i.e., incomplete ossification of the skull bone, sternebra, metacarpal, and talus-calcaneus). This safety margins for embryo-foetal toxicity are considered of potential relevance for use in humans, given that women of childbearing potential are included within the target population susceptible to be treated with vibegron.

However, given that therapeutic dose of vibegron is well specified in the Product Information, that the Product Information includes recommendations not to use vibegron in women of childbearing potential not using contraception and in pregnant women, and to stop the drug when pregnancy is planned or diagnosed, the expected impact on benefit-risk is limited.

Missing Information:

There is no missing information for Obgemsa.

SVII.2. New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3. Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important identified risks:

None

Important potential risks:

Embryo-foetal toxicity

Potential mechanisms:

Rabbits' studies showed that there was no evidence of developmental toxicity of vibegron in the 30-mg/kg/day or 100-mg/kg/day groups. However, in the 300-mg/kg/day group, there was a vibegron-related decrease in mean live foetal weight (14% and 9% below the control group in female and male foetuses, respectively) that was associated with a slightly increased incidence of foetuses with sites of incompletion ossification (i.e., incomplete ossification of the skull bone, sternebra, metacarpal, and talus-calcaneus). These observations are likely to be secondary to maternal toxicity observed in rabbits treated at 300 mg/kg/day (reduced mean maternal food consumption on GD 8 and 13, 30% and 21% below the control group, respectively). It is well documented that reduced foetal weights and incomplete ossification can resolve after delivery without impacting neonate development and post-natal skeletal development [CARNEY, 2007; DASTON, 2007].

In the study in rats, there was no evidence of developmental toxicity in the 30-, 100-, or 300-mg/kg/day groups. Of note, the highest tested dose of 1000 mg/kg/day induced unacceptable maternal toxicity (body weight losses and deaths) but without developmental toxicities. However, the safety margin for embryo-foetal toxicity based on the rat teratology study may be 78-times lower due to the lower potency of vibegron to the β3-AR for rats when compared to humans.

Evidence source and strength of evidence:

No adequate and well-controlled clinical studies have been conducted in pregnant women. Data in rabbits have shown embryo-foetal toxicity at high doses; delayed foetal skeletal ossification and reduced foetal body weights were observed in rabbits at approximately 898-fold clinical exposure (AUC). Although the safety margin for embryo-toxicity in the rabbit based on the NOAEL of 100 mg/kg/day was 285-fold greater than clinical exposure at the recommended daily dose of vibegron, embryo-foetal toxicity is considered as a potential risk in humans because of the 9-times lower potency of vibegron to the β3-AR for rabbits when compared to humans.

There is a potential for human embryo-foetal toxicity due to vibegron, hence embryo-foetal toxicity is considered as an important potential risk.

Characterization of the risk:

Frequency

No patient became pregnant under treatment in the vibegron arm while participating in the pivotal clinical studies (study 3003 and study 3004). One patient in Study 3003, who was randomised to placebo became pregnant between the End of Treatment Visit and the Follow-up Visit. The pregnancy went to term with a normal vaginal delivery. The outcome was reported as a live birth of a normal baby.

However, two patients have become pregnant during clinical studies other than pivotal studies, and are detailed below:

• In Study 008, 1 patient (receiving vibegron 100 mg + tolterodine) became pregnant during the extension study and discontinued from the study (Day 236). The pregnancy outcome was a healthy normal baby born by Caesarean section.

• In the completed IBS Study 2001, 1 patient (in vibegron 75 mg group) had an ectopic pregnancy. The patient had a positive pregnancy test approximately 1 month after initiating the study drug, which was then diagnosed as ectopic pregnancy, with no adverse events associated with the pregnancy reported. Ectopic pregnancy was terminated. No relevant medical history was reported except for history of Caesarean section. Ectopic pregnancy was considered not related to the study drug. No additional details were provided as the subject failed to respond to multiple attempts of contact.

In post-marketing experience, as of 20 September 2022, of the 4899 vibegron-related events reported overall in the post-marketing setting, there are 2 events related to pregnancy (PTs: pregnancy, and exposure during pregnancy; both non-serious) that were reported in post-marketing setting. These 2 events represent 0.04% of total post-marketing events.

Seriousness and severity:

No case of pregnancy was reported under vibegron treatment in the pivotal clinical studies.

In post-marketing setting, 2 events relevant to exposure during pregnancy (PTs: pregnancy, and exposure during pregnancy); both were non-serious.

Absolute risk:

Not applicable

Reversibility:

There is no clinical data of embryo-foetal toxicity available in human as no adequate and well-controlled clinical studies have been conducted in pregnant women. In animal studies, reduced foetal weights and delayed ossifications were seen to be reversible after birth [CARNEY, 2007; DASTON, 2007].

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 daily dose of vibegron, in rats and rabbits, respectively. However, delayed foetal skeletal ossification and reduced foetal body weights were observed in rabbits at approximately

898-fold clinical exposure (AUC), the delayed ossifications are reversible and resorbed after birth, thus in most cases without consequences.

Long-term outcomes:
There is no available clinical data of embryo-foetal toxicity in human as no adequate and well-controlled clinical studies have been conducted in pregnant women. However, as a general aspect, the impact of the risk of embryo-foetal toxicity on the individual patient has the potential to be permanent, and in addition, has the potential to harm a foetus during pregnancy, producing a long-term effect. It is therefore recommended that Vibegron should not be administered during pregnancy, and to stop treatment with the drug in case of pregnancy is planned or diagnosed.

Impact on quality of life:
Embryo-foetal toxicity is likely to have an impact on quality of life, as the development of a foetus could be potentially affected.

Risk factors and risk groups:
The at-risk group for experiencing vibegron-related embryo-foetal toxicity includes female patients of child-bearing potential and developing foetuses who are exposed to Vibegron during gestation.

Preventability:
The preventability is addressed through the information included in the Product Information; preclinical findings observed in animals are mentioned in Section 5.3 of the SmPC. In addition, the section 4.6 of the SmPC includes recommendations not to use vibegron during pregnancy and in women of childbearing potential not using contraception, and treatment with vibegron should be stopped when pregnancy is planned or diagnosed. These recommendations are also included in the PL.

Impact on the risk-benefit balance of the product:
The potential risk of embryo-foetal toxicity is considered important due to the evidence resulting from the animal studies at approximately 1867 and 898-fold greater than the clinical exposure in humans, in rats and rabbits respectively. Nevertheless, as vibegron showed 9 and 78-times lower in vitro β3-AR potency for rabbits and rats, respectively, when compared to humans, potential β3-AR-mediated effects may occur at lower systemic exposures than for non-β3-AR-related effects. Given that the therapeutic dose of vibegron is well specified in the Product Information, that there are recommendations not to use vibegron in women of childbearing potential not using contraception and in pregnant women, as well as to stop the drug when pregnancy is planned or diagnosed, the expected impact on benefit-risk is limited.

Public health impact:

Public health impact would be relevant for patients whose quality of life is impacted by the development of embryo-foetal toxicity. However, considering the absence of the events of interest being reported under vibegron treatment in the clinical studies, that the therapeutic dose is well specified in the Product Information, in addition to the recommendations included in the Product Information about use of vibegron in women of childbearing potential, the impact on public health is deemed limited.

SVII.3.2. Presentation of the missing information

None

Part II: Module SVIII - Summary of the safety concerns

Table 11: Summary of Safety Concerns

Important identified risks	None
Important potential risks	Embryo-foetal toxicity
Missing information	None

Part III: Pharmacovigilance plan (including post-authorisation safety studies)

III.1. Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond ADR reporting and signal detection:

Specific follow-up form for drug exposure during pregnancy is used as part of the routine pharmacovigilance activities to document and follow up any adverse event occurring during pregnancy after drug exposure (See Annex 4).

A second follow-up form used by the MAH as a general routine pharmacovigilance activity (beyond ADR reporting and signal detection) specific to document any adverse event in the newborn being exposed to the drug during intrauterine life or via breastmilk will be applicable to follow up the potential risk of embryo-foetal toxicity (See Annex 4).

Specific adverse reaction follow-up questionnaires

The following specific follow up forms are provided in Annex 4:

- VIGILANCE CASE DOCUMENTATION FORM: PREGNANCY FOLLOW-UP AFTER DRUG EXPOSURE
- VIGILANCE CASE DOCUMENTATION FORM: CHILDBIRTH AFTER A DRUG EXPOSURE DURING PREGNANCY OR EXPOSURE VIA BREASTFEEDING

Other forms of routine pharmacovigilance activities

None.

III.2. Additional pharmacovigilance activities

No additional pharmacovigilance activities are warranted.

III.3. Summary table of additional pharmacovigilance activities

No additional pharmacovigilance activities are planned to be conducted.

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

V.1. Routine risk minimisation measures

Routine risk minimisation measures are described for the safety concerns in Table Part V.1 below:

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risk	
None	Not applicable
Important potential risk	
Embryo-foetal toxicity	**Routine risk communication:** - SmPC section 4.6 and section 5.3 - PL section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** - In SmPC section 4.6, it is indicated that vibegron is not recommended in women of childbearing potential not using contraception. In addition, it is explained that reproductive toxicity has been observed in animal studies and vibegron is not recommended during pregnancy. When pregnancy is planned or diagnosed, treatment with vibegron should be stopped. - In PL section 2, recommendations are included for women in childbearing potential in case of pregnancy or planned pregnancy. **Other routine risk minimisation measures beyond the Product Information:** Legal status: restricted medical prescription
Missing information	
None	Not applicable

PL = Package leaflet; SmPC = Summary of Product Characteristics.

V.2. Additional risk minimisation measures

No additional risk minimisation measures have been identified.

V.3. Summary of risk minimisation measures

Table Part V.3 below presents the summary of pharmacovigilance activities and risk minimisation activities for safety concerns of vibegron.

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk		
None	Not applicable	Not applicable
Important potential risk		
Embryo-foetal toxicity	Routine risk minimisation measures: - SmPC section 4.6 and section 5.3: - PL section 2 Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up forms Additional pharmacovigilance activities: None.
Missing information		
None	Not applicable	Not applicable

PL = Package leaflet; SmPC = Summary of Product Characteristics.

Part VI: Summary of the risk management plan

Summary of risk management plan for Obgemsa (vibegron)

This is a summary of the risk management plan (RMP) for Obgemsa. The RMP details important risks of Obgemsa, how these risks can be minimised, and how more information will be obtained about Obgemsa risks and uncertainties (missing information).

Obgemsa summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Obgemsa should be used.

This summary of the RMP for Obgemsa should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Obgemsa RMP.

I. The medicine and what it is used for

Obgemsa is authorised for symptomatic treatment of adult patients with overactive bladder (OAB) syndrome (see SmPC for the full indication). It contains vibegron as the active substance and is intended for oral administration.

Further information about the evaluation of Obgemsa benefits can be found in Obgemsa EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary>.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Obgemsa, together with measures to minimise such risks and the proposed studies for learning more about Obgemsa risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Obgemsa are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Obgemsa. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	Embryo-foetal toxicity
Missing information	None

II.B Summary of important risks

Important identified risk	None
Important potential risk: Embryo-foetal toxicity	
Evidence for linking the risk to the medicine	No adequate and well-controlled clinical studies have been conducted in pregnant women. Data in in rabbits have shown embryo-foetal toxicity at high doses; delayed foetal skeletal ossification and reduced foetal body weights were observed in rabbits at approximately 898-fold clinical exposure (AUC). Although the safety margin for embryo-toxicity in the rabbit based on the NOAEL of 100 mg/kg/day was 285-fold greater than clinical exposure at the recommended daily dose of vibegron, embryo-foetal toxicity is considered as a potential risk in humans because of the 9-times lower potency of vibegron to the β3-AR for rabbits when compared to humans. There is a potential for human embryo-foetal toxicity due to vibegron, hence embryo-foetal toxicity is considered as an important potential risk.
Risk factors and risk groups	Female patients of child-bearing potential and developing foetuses who are exposed to vibegron during gestation.
Risk minimisation measures	Routine risk minimisation measures: - SmPC section 4.6 and section 5.3: - PL section 2 Additional risk minimisation measures: None.
Missing information	None

II.C Post-authorisation development plan

II.C.1. Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Obgemsa.

II.C.2. Other studies in post-authorisation development plan

There are no studies required for Obgemsa.

Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

Specific follow-up form for drug exposure during pregnancy is used as part of the routine pharmacovigilance activities to document and follow up any adverse event occurring during pregnancy after drug exposure.

A second follow-up form used by the MAH as a general routine pharmacovigilance activity (beyond ADR reporting and signal detection) specific to document any adverse event in the newborn being exposed to the drug during intrauterine life or via breastmilk will be applicable to follow up the potential risk of embryo-foetal toxicity.

The following follow-up forms are provided in this annex:

- Vigilance case documentation form: pregnancy follow-up after drug exposure

- Vigilance case documentation form: childbirth after a drug exposure during pregnancy or exposure via breastfeeding

VIGILANCE CASE DOCUMENTATION FORM: PREGNANCY FOLLOW-UP AFTER DRUG EXPOSURE

File no. |__|__|__|__|- |__|__|__|__|__| (For Laboratory use only)

Part A

Reporter

Name [i/ii]:_____ ❑ Health professional: ❑ Gynecologist
Address: ❑ General practitioner
_____ ❑ Pharmacist
_____ ❑ Other: _____
_____
❑ Patient
Tel: _____ ❑ Other: _____

Patient treated

Last name (first 3 letters): |__|__|__| First name (1st letter): |__|
Date of birth ___/___/___ or Age: _____
Height: _____ cm Weight: _____ kg

Medication was taken:
❑ By the mother
❑ By the father

Mother's Medical history

Previous and current diseases, and operations (Specify the start dates if possible) :

❑ Arterial hypertension ___/___/___ ❑ On-going
❑ Diabetes ___/___/___ ❑ On-going
❑ Epilepsy ___/___/___ ❑ On-going
❑ Smoker ____ cig/day ___/___/___ ❑ On-going
❑ Alcohol ___/___/___ ❑ On-going
❑ Drug addiction ___/___/___ ❑ On-going
❑ Unknown

Other:
_____
_____
_____

Previous immunisation:

Rubella: ❑ YES ❑ NO ❑ Unknown
Toxoplasmosis: ❑ YES ❑ NO ❑ Unknown
CMV: ❑ YES ❑ NO ❑ Unknown
❑ Positive Rhesus ❑ Negative Rhesus
Other: _____

Medical history, obstetrics and gynecology:
_____
_____
_____

Medical history in the family:
(Including age and rhesus of the father)
_____
_____
_____

Suspected Pierre Fabre product*

Name of the Pierre Fabre suspected medication / the product:
_____
Route of administration: _____
(oral, applied to the skin...)
Indication: _____
Dose/day: _____

**Complete with real product intake (not prescribing information)*
Start date of treatment: ___/___/___
End date of treatment: ___/___/___
Treatment duration: _____
On-going treatment ❑
Batch number: _____
Expiry date: ___/___/___
Associated quality claim: ❑ YES ❑ NO

Associated medications /

Name	Reason for use	Dose/day	Start date of treatment	End day of treatment

Part B

Pregnancy follow

Date of Last Menstrual: ___/___/___ Weeks of gestational age on reporting date: _____

Start of pregnancy (confirmed by ultrasound): ___/___/___ Delivery date was scheduled on: ___/___/___

Trimester of exposure: ❑ First ❑ Second ❑ Third

❑ Amniocentesis - Date: ___/___/___

Results:_____

_____

_____

Growth retardation in utero: ❑ YES ❑ NO If yes, specify:

_____

_____

_____

Part C (this part should be reported if an adverse event or a specific situation are associated)

Associated adverse event

Nature of the adverse effect associated:	Start date or time of onset (day/month)	End date	On-going
_____	_____	_____	❑
_____	_____	_____	❑
_____	_____	_____	❑

Results of additional examinations *(possibly performed following the adverse effect(s) (if possible, attach a photocopy of ultrasound reports, hospitalisation reports and/or the additional examinations performed)*

_____

_____

_____

Actions taken

A general practitioner or gynecologist was consulted?

❑ YES ❑ NO

If yes, please indicate the physician's surname, first name and practice address

_____

Did the adverse effect require corrective treatment?

❑ YES ❑ NO If yes, why? _____

Following the occurrence of the adverse effect, the dose of the medicine/Pierre Fabre product has been:

❑ decreased ❑ increased ❑ Unchanged ❑ stopped

Was the Pierre Fabre product used again? ❑ YES ❑ NO (indicate the date of resumption: ___/___/___)

If yes, has the adverse effect recurred? ❑ YES ❑ NO

(indicate the recurrence date of the effect: ___/___/___)

Specific situation

❑ **Abuse** *(Intentional excessive use)*

❑ **Overdose** *(Administration of a quantity of medication above the recommended maximum dose)*

❑ ***Misuse*** *(medication used intentionally and inappropriately)*

❑ **Medication error**[1] *(Unintentional error)*

❑ **Occupational exposure** *(Exposure to a medication as part of your work)*

❑ **Unexpected therapeutic benefit**

❑ **Off label use**

❑**Therapeutic inefficacy**

Progression

❑ Recovered - Date: ___/___/___

❑ without sequelae

❑ with sequelae

❑ Patient recovering

❑ Patient not recovered

❑ Death

❑ Unknown

❑ Impact on daily life (stopped working, unable to leave home,...) ❑ YES ❑ NO

Specify: _____

Severity

❑ Not serious

❑ Other serious medical situation, specify:

_____

❑ Hospitalisation (or prolongation of hospitalisation) from ___/___/___ to ___/___/___

❑ Incapacity or permanent disability

❑ Congenital anomaly or malformation *(present at birth)*

❑ Life-threatening *(risk of death)*

❑ Death: on ___/___/___

Description of the pharmacovigilance case	
***Specify the chronology and progression of the clinical disorders and laboratory parameter abnormalities with dates, for example**:* *- after the onset of the adverse effect, if one (or several) medication(s) were discontinued (specify which)* *- if there was disappearance of the effect after discontinuation of the medication(s) (specify which)* *- if one or several medications have been reintroduced (specify which) with progression of the adverse effect after reintroduction.* *Where applicable, specify the conditions of onset of the adverse effect (normal conditions of use, medication error, overdose, misuse, abuse, adverse effect linked to occupational exposure).*	**[1]In the case of medication error** (unintentional) **Nature** ❑ Risk of error ❑ Potential error ❑ Proven error **Cause of the error** ❑ Confusion about the brand name: _____ ❑ Illegibility of the information on the label: _____ ❑ Lack of information (SPC, leaflet): _____ ❑ Lack of packaging (box etc…): _____ ❑ Other Specify: _____
Has this case been notified to the Competent Authorities? ❑ YES ❑ NO	
Date: _____ Signature:	

Thank you for agreeing to complete this Pharmacovigilance form, Best regards.

[i] In European Economic Area (EEA) - INFORMATION FOR THE REPORTER: The data collected about you will be subject to data processing in accordance with the provisions of the General Data Protection Regulation (GDPR) of April 27, 2016. All information and personal data that you share with us via this form will be protected and will remain confidential in accordance with our company policy and the regulation in force. The information you provide will be used for safety monitoring and may be shared with health authorities, the processing of your personal data being necessary for compliance with a legal obligation to which Pierre Fabre is subject. Please note that this personal data will be deleted or anonymized 50 years after marketing authorization withdrawal of our products. You have a right of access, rectification and restriction of processing of your personal data. You can exercise these rights by contacting us at generic email address *(local GDPR contact to be completed)*. You have the right to lodge a complaint with the national supervisory authority in charge of protection of personal data *(name to be completed)*.

[ii] Out of European Economic Area (EEA) - INFORMATION FOR THE REPORTER P*lease adapt the above section i "INFORMATION FOR THE REPORTER" if applicable according to the local data privacy regulation.*

VIGILANCE CASE DOCUMENTATION FORM: CHILDBIRTH AFTER A DRUG EXPOSURE DURING PREGNANCY OR EXPOSURE VIA BREASTFEEDING

File no. |__|__|__|__|__|- |__|__|__|__|__| (For Laboratory use only)

Part A

Reporter

Name [ii/ii]: _____

Address:_____

_____

_____

_

Tel: _____

❑ Health professional: ❑ Gynecologist
❑ General practitioner
❑ Pharmacist
❑ Other: _____

❑ Patient

❑ Other: _____

Mother

Last name (first 3 letters): |__|__|__| First name (1st letter): |__| Date of birth ___/___/___ or Age: _____

Height: _____ cm Weight : _____ kg

Medication was administered:

❑ By the mother during pregnancy in _____ trimester

❑ By the mother during breastfeeding

❑ transmission via father

Suspected Pierre Fabre Product*

Product name: _____

Route of administration: _____

(oral, applied to the skin…)

Indication: _____

Dose/day: _____

**Complete with real product intake (not prescribing information)*

Start date of treatment: ___/___/___

End date of treatment: ___/___/___

Treatment duration _____

On-going treatment ❑

Batch number: _____ Expiry date: ___/___/___

Associated quality claim: ❑ YES ❑ NO

Associated medications

Name	Reason for use	Dose/day	Start date of treatment	End day of treatment

Part B

Childbirth

Delivery date: ___/___/___ Weeks of gestational age on delivery date : _____

Delivery type:

❑ Spontaneous vaginal delivery
❑ Caesarean
❑ spontaneous abortion
❑ Induced abortion
❑ Unknown

Birth type:

❑ Born alive
❑ Full-term
❑ Premature
❑ Post-term
❑ Intrauterine death
❑ Post mature
❑ Outcome pending
❑ Unknown

Newborn information:

❑ Normal
❑ Malformation
Specify: _____
❑ Unknown
❑ Perinatal complication
❑ Post perinatal complication
❑ Dysmature
❑ Born death
Specify: _____

Height: _____cm
Weight: _____g
APGAR score at 5 minutes: _____
Head circumference: _____

Heart condition: _____
Respiratory condition: _____
Psychomotor condition: _____

Part C

Breastfeeding

The child was breastfeed: ❑ YES ❑ NO

Breastfeeding is on-going: ❑ YES ❑ NO If no, specify breastfeeding time : _____

❑ exclusive breastfeeding

❑ mixed feeding Frequency: _____ suckled/day

_____ baby bottle/day

Part D (this part should be reported if an adverse event or a specific situation are associated)

Associated adverse event

Nature of the adverse effect associated	Start date or time of onset (day/month)	End date	On-going
_____	_____	_____	❑
_____	_____	_____	❑

Results of additional examinations *(possibly performed following the adverse effect(s) (if possible, attach a photocopy of ultrasound reports, hospitalisation reports and/or the additional examinations performed)*

_____
_____
_____

Actions taken

A general practitioner or gynecologist was consulted?

❑ YES ❑ NO

If yes, please indicate the physician's surname, first name and practice address

_____

_____

Did the adverse effect require corrective treatment?

❑ YES ❑ NO If yes, why? _____

Following the occurrence of the adverse effect, the dose of the medicine/Pierre Fabre product has been:

❑ decreases ❑ increases ❑ Unchanged ❑ stopped

Was the Pierre Fabre product used again? ❑ YES ❑ NO (indicate the date of resumption: ___/___/___)

If yes, has the adverse effect recurred? ❑ YES ❑ NO

(indicate the recurrence date of the effect: ___/___/___)

Specific situation

❑ **Abuse** *(Intentional excessive use)*

❑ **Overdose** *(Administration of a quantity of medication above the recommended maximum dose)*

❑ **Misuse** *(medication used intentionally and inappropriately)*

❑ **Medication error**[1] *(Unintentional error)*

❑ **Occupational exposure** *(Exposure to a medication as part of your work)*

❑ **Unexpected therapeutic benefit**

❑ **Off label use**

❑ **Therapeutic inefficacy**

Progression

❑ Recovered - Date: ___/___/___

❑ without sequelae

❑ with sequelae

❑ Patient recovering

❑ Patient not recovered

❑ Death

❑ Unknown

❑ Impact on daily life (stopped working, unable to leave home,...) ❑ YES ❑ NO

Specify: _____

Severity

❑ Non serious

❑ Other serious medical situation

Specify: _____

❑ Hospitalisation (prolongation)

from ___/___/___ to ___/___/___

❑ Incapacity or permanent disability

❑ Congenital anomaly or malformation *(present at birth)*

❑ Life-threatening *(risk of death)*

❑ Death: on ___/___/___

DESCRIPTION OF THE PHARMACOVIGILANCE CASE	
***Specify the chronology and progression of the clinical disorders and laboratory parameter abnormalities with dates, for example**:* *- after the onset of the adverse effect, if one (or several) medication(s) were discontinued (specify which)* *- if there was disappearance of the effect after discontinuation of the medication(s) (specify which)* *- if one or several medications have been reintroduced (specify which) with progression of the adverse effect after reintroduction.* *Where applicable, specify the conditions of onset of the adverse effect (normal conditions of use, medication error, overdose, misuse, abuse, adverse effect linked to occupational exposure).*	**[1]In the case of medication error** (unintentional) **Nature** ❑ Risk of error ❑ Potential error ❑ Proven error **Cause of the error** ❑ Confusion about the brand name: _____ ❑ Illegibility of the information on the label: _____ ❑ Lack of information (SPC, leaflet): _____ ❑ Lack of packaging (box etc…): _____ ❑ Other Specify: _____
Has this case been notified to the Competent Authorities? ❑ YES ❑ NO	
Date: _____ Signature:	
Thank you for agreeing to complete this Pharmacovigilance form, Best regards,	

[i] In European Economic Area (EEA) - INFORMATION FOR THE REPORTER: The data collected about you will be subject to data processing in accordance with the provisions of the General Data Protection Regulation (GDPR) of April 27, 2016. All information and personal data that you share with us via this form will be protected and will remain confidential in accordance with our company policy and the regulation in force. The information you provide will be used for safety monitoring and may be shared with health authorities, the processing of your personal data being necessary for compliance with a legal obligation to which Pierre Fabre is subject. Please note that this personal data will be deleted or anonymized 50 years after marketing authorization withdrawal of our products. You have a right of access, rectification and restriction of processing of your personal data. You can exercise these rights by contacting us at generic email address *(local GDPR contact to be completed)*. You have the right to lodge a complaint with the national supervisory authority in charge of protection of personal data *(name to be completed)*.

[ii] Out of European Economic Area (EEA) - INFORMATION FOR THE REPORTER P*lease adapt the above section i "INFORMATION FOR THE REPORTER" if applicable according to the local data privacy regulation.*

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable