NOVARTIS

Chief Medical Office & Patient Safety

Ondansetron

ODT032

EU Safety Risk Management Plan

Active substances (INN or common name):	Ondansetron, Ondansetron hydrochloride dihydrate
Products concerned (brand names):	ZOFRAN™, ZYDIS™
Document status:	Final
Version number:	6.0
Data lock point for this RMP	28-Feb-2021 (PSUR reporting period: 01-Mar-2018 to 28-Feb-2021)
Date of final sign off	28-Apr-2022

Template version 6.3, Effective from 24-Feb-2021

Rationale for submitting an updated RMP:

The following safety concerns provided in Risk Management Plan (RMP) version (v) 5.1 are proposed to be removed based on guidelines of Good Pharmacovigilance Practices (GVP) Module V (Revision 2).

- **Important identified risks:**
  - Profound hypotension and loss of consciousness when administered with apomorphine hydrochloride
  - Hypersensitivity
  - QT interval prolongation and Torsade de Pointes (TdP)
  - Toxic skin eruption, including Toxic Epidermal Necrolysis (TEN)
- **Important potential risks:**
  - Serotonin syndrome
  - Reduced clearance and prolonged half-life in patients with hepatic impairment
  - Sub-acute intestinal obstruction in patients with impaired gastrointestinal motility
  - Adverse events in breast-fed infants due to use of ondansetron during lactation
- **Missing information:**
  - Safety in pregnant women
- **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**
  - Specific adverse reactions follow-up checklists for Hypersensitivity including Anaphylaxis, QT interval prolongation or Torsade de Pointes, and Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis are proposed to be removed.

Summary of significant changes in this RMP:

This RMP update is carried out in the new RMP template in accordance with GVP Module V (Revision 2):

Part	Major changes in v 6.0 compared to RMP v 5.1
Part I	Updated the section as per the product information (PI) and core data sheet (CDS) v1.3 dated 10-Mar-2021
Part II Module SI	None
Part II Module SII	None
Part II Module SIII	None
Part II Module SIV	None
Part II Module SV	Updated the post-authorization exposure in alignment with Periodic Safety Update Report (PSUR) (reporting period: 01-Mar-2018 to 28-Feb-2021)
Part II Module SVI	None

Part II Module SVII	Removal of below-mentioned safety concerns with rationale for the change: **Important identified risks**: • Profound hypotension and loss of consciousness when administered with apomorphine hydrochloride • Hypersensitivity • QT interval prolongation and Torsade de Pointes • Toxic skin eruption, including Toxic Epidermal Necrolysis **Important potential risks**: • Serotonin syndrome • Reduced clearance and prolonged half-life in patients with hepatic impairment • Sub-acute intestinal obstruction in patients with impaired gastrointestinal motility • Adverse events in breast-fed infants due to use of ondansetron during lactation **Missing information**: • Safety in pregnant women Updated the details under “Evidence sources and strength of evidence” and “Characterization of the risk” in “Table 8-1 – Important potential risk – Adverse birth outcomes following use during pregnancy: Other details” with citation of two new references.
Part II Module SVIII	Updated the existing list of the summary of safety concerns
Part III	Updated Section 10.1.1 – “Routine pharmacovigilance activities beyond ADRs reporting and signal detection" by removal of all specified adverse reactions follow-up checklists, as not applicable.
Part IV	None
Part V	Updated the information on routine risk minimization activities for the important potential risk – “Adverse birth outcomes following use during pregnancy” in Table 12-1 and Table 12-2
Part VI	Updated the summary of risk management plan in accordance with the updates made in preceding sections
Part VII Annexes	
Annex number	**Description of changes**
Annex 1	None
Annex 2	Updated the category number of the completed study in Table 14-2
Annex 3	Administrative update as per new RMP template in accordance to the GVP Module V (Revision 2)
Annex 4	Removed specific adverse reactions follow-up checklists
Annex 5	None
Annex 6	None
Annex 7	None
Annex 8	Updated the Summary of changes to the RMP v6.0

Other RMP versions under evaluation

No RMP versions are currently under evaluation.

Details of the currently approved RMP:

Version number & date: 5.1 dated 18-Mar-2016

Data lock point for RMP v5.1: 31-May-2015

QPPV name: [redacted]

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the Marketing Authorization Holder's (MAH´s) QPPV. The electronic signature is available on file.

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List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
CDS	Core Data Sheet
CI	Confidence Interval
CINV	Chemotherapy-Induced Nausea and Vomiting
COPD	Chronic Obstructive Pulmonary Disease
CT	Clinical Trial
DDD	Defined Daily Dose
DLP	Data Lock Point
EEA	European Economic Area
EU	European Union
GSK	GlaxoSmithKline
GVP	Good Pharmacovigilance Practices
HEC	Highly Emetogenic Chemotherapy
5HT	5-hydroxytryptamine (serotonin)
INN	International Nonproprietary Names
IV	Intravenous
kg	Kilogram
LEC	Low emetogenic chemotherapy
MEC	Moderately emetogenic chemotherapy
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
minEC	Minimally emetogenic chemotherapy
mL	Milliliter
PhV	Pharmacovigilance
PONV	Post-operative nausea and vomiting
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PTY	Patient Treatment Years
RINV	Radiotherapy Induced Nausea and Vomiting
RMP	Risk Management Plan
RR	Relative Risk
ROW	Rest of the world
SAE	Serious Adverse Event
TdP	Torsade de Pointes
TEN	Toxic Epidermal Necrolysis

1 Part I: Product Overview

Table 1-1 Part I.1 – Product Overview

Active substance(s) (INN or common name)	Ondansetron, Ondansetron hydrochloride dihydrate
Pharmacotherapeutic group(s) (ATC Code)	Selective $5HT_3$ (5-hydroxytryptamine) receptor antagonist (A04AA, A04AD)
Marketing Authorization Holder	Novartis Europharm Limited
Medicinal products to which this RMP refers	1
Invented names in the European Economic Area (EEA)	ZOFRAN™, ZYDIS™, Ondansetron Zydis, Ondansetron, Ondanoglax Zydis, Ondanoglax, Glaxosetron, Glaxosetron Zydis, Avessaron, Zofran, Zofran Preserved, ZOPHREN, Aodrin, Zamanol, Ceramos, Ceramos Zydis, Ondansetron Zydis Lingual, Ondansetron GSK, Zofron, Zofron Zydis, Ondansetron Hydrochloride Zydis, Sarevan, Ondansetron Ratiopharm_GEN, Ondansetron GSK 4 mg, Ondansetron Allen 8 mg, Ondansetron Allen 4 mg, Ondansetron Allen_GEN, Zofran Munloslig, Ondansetron GSK, Ondansetron GlaxoSmithKline
Marketing authorization procedure	National
Brief description of the product	**Chemical class**: Ondansetron is a potent, highly selective $5HT_3$ receptor antagonist.
	Summary of mode of action: Ondansetron is a potent, highly selective 5HT3 receptor antagonist. Its precise mechanism of action in the control of nausea and vomiting is not known. Chemotherapeutic agents and radiotherapy may cause release of 5HT in the small intestine initiating a vomiting reflex by activating vagal afferents via 5HT3 receptors. Ondansetron blocks the initiation of this reflex. Activation of vagal afferents may also cause a release of 5HT in the area postrema, located on the floor of the fourth ventricle, and this may also promote emesis through a central mechanism. Thus, the effect of ondansetron in the management of the nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy is probably due to antagonism of 5HT3 receptors on neurons located both in the peripheral and central nervous system.
	Important information about its composition: Tablets: Each tablet contains ondansetron 4 mg/8 mg as hydrochloride dihydrate. Syrup: Each 5 mL contains 4 mg ondansetron as hydrochloride dihydrate. Oral Lyophilizate (Zydis): The fast-dispersing oral dosage form contains 4 mg/8 mg ondansetron. Injection: Each 1 mL of aqueous solution contains 2 mg ondansetron as hydrochloride dihydrate. Suppositories: Each suppository contains 16 mg of ondansetron.
Indications in the EEA	Current: **Adults:** Oral Formulations: • Management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy (Chemotherapy-induced nausea and vomiting [CINV]/ Radiotherapy induced nausea and vomiting [RINV]) • Prevention of post-operative nausea and vomiting (PONV) Injection: • Management of CINV/RINV

	• Prevention and treatment of PONV Suppositories: • Management of CINV/RINV. **Pediatric populations:** Oral Formulations: • Management of CINV Injection: • Management of CINV • Prevention and treatment of PONV Suppositories: • Not indicated
	Proposed: Not applicable
Dosage in the EEA	Current recommended dosage: **Adults (for CINV/RINV):** Oral: 8 mg taken 1 to 2 hours before chemotherapy or radiation treatment, followed by 8 mg orally every 12 hours for a maximum of 5 days. Injection: 8 mg administered immediately before treatment. For highly emetogenic chemotherapy, a maximum initial ondansetron dose of 16 mg intravenous (i.v.) infused over 15 minutes may be used. Suppositories: One 16 mg suppository given 1 to 2 hours before treatment. **Adults (for PONV):** Oral: 16 mg given 1 hour prior to anesthesia. Injection: A single dose of 4 mg by IM or slow IV injection administered at the induction of anesthesia. **Pediatric populations (for CINV):** Oral and Injection: The dose can be calculated based on body surface area or weight. Suppositories: Not recommended in children. **Pediatric populations (for PONV):** Injection: For prevention and treatment of PONV in pediatric patients having surgery performed under general anesthesia, ondansetron may be administered by slow i.v. injection (not less than 30 seconds) at a dose of 0.1 mg/kg up to a maximum of 4 mg either prior to, at or after induction of anesthesia, or after surgery. **Elderly populations (for CINV and RINV)** Oral: No alteration of oral dose or frequency of administration is required. Injection: In patients 65 years of age or older, all IV doses should be diluted and infused over 15 min and, if repeated, given no less than 4 h apart. **Elderly populations (for PONV)** There is limited experience in the use of ondansetron in the prevention and treatment of PONV in the elderly, however ondansetron is well tolerated in patients over 65 years receiving chemotherapy.
	Proposed: Not Applicable
Pharmaceutical forms and strengths	**Pharmaceutical forms**: Current: • Oral route: Tablet, syrup, oral lyophilizate • Injectable route: Injection or infusion • Rectal route: Suppositories

	Strengths: Current: • Tablets: 4 mg, 8 mg • Syrup: 4 mg/5 mL • Oral Lyophilizate (Zydis): 4 mg, 8 mg • Injection solution: 2 mg/mL • Suppositories: 16 mg Different strengths may be available outside the EU.
	Proposed: Not applicable
Is the product be subject to additional monitoring in the EU?	No

2 Part II Safety specification Module SI: Epidemiology of the indications and target population

2.1 Indication: Chemotherapy induced nausea and vomiting

Incidence and prevalence:

The incidence of CINV is mainly determined by the emetogenic potential of the administered chemotherapy; but can be influenced by patient characteristics and the dose and efficacy of the prescribed antiemetic (Schnell 2003). In general, minimally emetogenic chemotherapy (minEC) is associated with emesis in < 10% of the patients treated with minEC, low emetogenic chemotherapy (LEC) is associated with emesis in 10-30%, moderately emetogenic chemotherapy (MEC) with 30-90%, and highly emetogenic chemotherapy (HEC) with more than 90% of the patients (Beckwith and Mullin 2001). Current clinical guidelines for management of CINV recommend prophylaxis with antiemetic medications and for most patients, antiemetic regimens prevent emesis and lessen nausea while patients are undergoing cancer therapy (Roila et al 2010, Basch et al 2011a, Ettinger et al 2012). However, some patients continue to report nausea and although >90% of patients receive antiemetic prophylactically the overall CINV frequency in actual routine European practice has been reported at 43-67% (Glaus et al 2004, Ihbe-Heffinger et al 2004, Ballatori et al 2007, Majem et al 2011), with a lower incidence during the "acute" 24-hr period (33-37%) compared to the "delayed" 2 to 7 day period (57-61%) following chemotherapy administration (Ihbe-Heffinger et al 2004, Ballatori et al 2007). The predominance of CINV during the delayed phase is also seen in other studies (Grunberg et al 2004, Molassiotis et al 2008, Hilarius et al 2012), which report acute and delayed nausea and vomiting as four distinct entities-the incidence during the first chemotherapy treatment cycle ranged from 35-39% for acute nausea, 47-68% for delayed nausea, 12-16% for acute vomiting, and 15-32% for delayed vomiting. The incidence of acute and delayed CINV also varies according to the emetogenicity of the chemotherapeutic agent (see Table 2-1). HEC-treated patients have a higher frequency of acute nausea, whereas MEC-treated have slightly higher frequencies of acute and delayed vomiting. Though based on small sample sizes, CINV rates for minEC- and LEC-treated patients are typically lower than those of the HEC- and MEC-treated patients. Caution should be taken in interpretation, however, as the range of frequencies are wide and the cytotoxic chemotherapeutic agents and antiemetic treatment strategies varied widely across studies.

Table 2-1 Range of estimated incidence of nausea and vomiting in chemotherapy-treated cancer patients reported in the literature, by emetogenicity of the administered antineoplastic

CINV	minEC*	LEC*	MEC	HEC
Acute nausea	33.3%	21.4%	22-54%	14-53%
Delayed nausea	33.3%	25%	33-75%	24-60%
Acute vomiting	7.1%	16.7%	0-22%	1-16%
Delayed vomiting	7.1%	0%	20-28%	17-50%

Source: Grunberg et al 2004, Molassiotis et al 2008, Majem et al 2011, Hilarius et al 2012
*Values for patients treated with minEC and LEC were reported in only 1 study (Molassiotis et al 2008)

Demographics of the target population in Chemotherapy induced nausea and vomiting – age, gender, racial and/or ethnic origin

Among the chemotherapy-treated cancer patients who were enrolled in 7 prospective, observational studies of CINV in routine European practice, the median or mean age of participants ranged from 54-61 years and the mean (range) percentage of participants who were female was 58.5% (31-78%) (Glaus et al 2004, Grunberg et al 2004, Ihbe-Heffinger et al 2004, Ballatori et al 2007, Molassiotis et al 2008, Majem et al 2011, Hilarius et al 2012).

Risk factors for the disease:

Factors that increase the risk of CINV include younger age (< 50 years), female gender, history of motion sickness, CINV during prior chemotherapy treatment, and history of pregnancy-related nausea and vomiting (Beckwith and Mullin 2001).

The main existing treatment options:

Current treatments to prevent CINV include serotonin receptor antagonists (ondansetron, granisetron, dolasetron, tropisetron, palonosetron), neurokinin receptor antagonists (aprepitant and fosaprepitant), dopamine receptor antagonists (metoclopramide and prochlorperazine) and corticosteroids (dexamethasone). These medications are given alone or in combination as prophylaxis for CINV; the regimen varies depending on the emetogenicity of the chemotherapy (Hesketh 2008).

Natural history of the indicated condition in the target population, including mortality and morbidity:

Chemotherapy-induced nausea and vomiting negatively impacts patients' quality of life and can lead to poor compliance or dose reductions in chemotherapy, imbalance in metabolism, nutrient depletion, anorexia, wound re-opening, and esophageal tear (Ballatori and Roila 2003).

Important co-morbidities found in the target population:

The overall cancer population receiving chemotherapy covers a wide range of types of cancers with a wide range of co-morbidities. Table 2-2 provides a list of cardiovascular comorbidities from a recent study of patients who received HEC and/or MEC therapy. The study was based on a US claims dataset and included HEC/MEC-treated patients for a selected set of cancers (breast, colorectal, head & neck, lung and ovarian cancers). Among patients with HEC and/or MEC and without antiemetic, the frequencies were highest for hypertension (18.26%) and arterial thromboembolic events (16.01%) (Vo and Nelson 2012).

Table 2-2 Cardiovascular events in patients with select cancers and less than four cycles of HEC and/or MEC combined

Cardiovascular and Thromboembolic Events*	N	%
Angina Pectoris	20	0.52
Arterial Disorder	3	0.08
Arterial Occlusive Disease	1	0.03
Arterial Thromboembolic (excludes chest pain/discomfort)	196	5.13
Arterial Thromboembolic (includes chest pain/discomfort)	611	16.01

Cardiovascular and Thromboembolic Events*	N	%
Cardiac Arrest	22	0.58
Cardiac Disorder	2	0.05
Cardio-respiratory Arrest	24	0.63
Cardiogenic Shock	1	0.03
Cerebral Ischemia	50	1.31
Cerebrovascular Accident	46	1.21
Chest pain or discomfort	488	12.78
Circulatory Collapse	11	0.29
Embolism	77	2.02
Hypertension	697	18.26
Hypotension	117	3.07
Iliac Artery Embolism	1	0.03
Increased platelets	6	0.16
Intermittent Claudication	5	0.13
Myocardial Infarction	11	0.29
Myocardial Ischemia	9	0.24
Peripheral Embolism	25	0.65
Peripheral Ischemia	0	
Sudden Death	0	
Syncope	96	2.52
Venous Thromboembolic	308	8.07

*2010 patients with breast, colorectal, head & neck, lung and ovarian cancers
Source: Vo and Nelson 2012.

2.2 Indication: Radiation-induced Nausea/vomiting

Incidence and prevalence:

Radiation-induced Nausea/vomiting is often considered to be less frequent and less severe than nausea/vomiting induced by chemotherapy, although the issue has only been addressed in a few studies (Dennis et al 2011). It is possible that nausea and vomiting after radiotherapy is often underestimated by physicians and untreated which can worsen patient's quality of life and may cause interruption of the treatment (Dennis et al 2012). It is therefore troubling that RINV are not considered as serious concerns by radiation oncologists (Horiot 2004). The newly updated guideline for antiemetics in oncology by the American Society of Clinical Oncology (ASCO) specifically highlights patients suffering from RINV as a special and understudied population (Basch et al 2011b).

Systematic review of published past observational studies (Medline search from Jan-2004 to Jun-2009) on RINV highlight that the overall cumulative incidence of vomiting and nausea (most studies looked at acute nausea and vomiting occurring within a day) is about 50-80% of patients undergoing radiotherapy (Feyer et al 2011). Two more recent prospective observational studies provide information on the frequency of RINV and the extent to which this problem is treated. In the latest NIS, the Italian Group for Antiemetic Research in Radiotherapy analyzed the incidence of RINV in 1020 patients receiving various kinds of radiotherapy. Overall, nausea and/or vomiting was reported by 28%. The median time to the first episode of vomiting was

3 days. Antiemetic drugs were administered to 17% of the patients, including 12% treated prophylactically and 5% given rescue therapy (Maranzano et al 2010).

In a cross-sectional study including 368 cancer patients aged +18 treated with (curative or palliative) radiotherapy at Swedish university hospitals, approximately one third of radiotherapy patients experienced nausea and vomiting during a typical week of treatment (39% experienced nausea and 7% vomited), but the vast majority (85%) were not prescribed antiemetics (Enblom et al 2009).

Demographics of the target population – age, gender, racial and/or ethnic origin

Among patients included in a cross-sectional study conducted in Sweden, younger patients experienced more nausea and vomiting compared to the older patients (relative risk: 1.9) (Enblom et al 2009). Italian study also reported that incidence of nausea in patients younger than 60 years is higher than those aged above 60 years (32.7% vs. 22.8%) (Maranzano et al 2010). Published observational studies did not show any significant differences between male and female patients. No ethnicity/race variation of target population is available from observational study.

Risk factors for the disease

In most recent Italian observational study, the irradiated site, radiation field size, and previous chemotherapy were significant risk factors for RINV. Patients with upper abdominal radiotherapy were at major risk of vomiting and nausea (50%), followed by those treated on the brain, thorax, head and neck, and pelvis (35%, 31%, 30.5% and 24% respectively) (Maranzano et al 2010).

In another Italian study including 934 cancer patients treated with radiotherapy between November to December 1996 (without concomitant chemotherapy), site of irradiation (upper abdomen) and field size (greater than 400 cm^2) showed significant association with RINV (ItalianGroup 1999).

Results of Swedish study also show that risk of RINV was higher in radiotherapy targeted to the pelvis/ abdominal field (relative risk [RR]: 2.0; 95% CI: 1.5-2.7), patients younger than 40 years (RR: 1.9; 95% CI: 1.3-2.7) and patients with prior experience of nausea (RR: 1.8; 95% CI: 1.3-2.5) (Enblom et al 2009).

An open-label study including 288 cancer patients conducted in Greece showed that risk of radiotherapy induced nausea was highly associated with the site of primary cancer, (lung and uterine cancer with odds ratio of 3.7 and 10.4, respectively). For vomiting, in addition to the primary cancer site, the risk was highly associated with metastasis status (yes vs. no odds ratio: 2.29), type of treatment (palliative vs. curative odds ratio: 1.62) and dose fraction (> 3 vs. < 3 with odds ratio: 1.94) (Mystakidou et al 2006).

The main existing treatment options

The pathophysiology of RINV is incompletely understood but is thought to be similar to that caused by chemotherapy. The treatment of CINV has therefore guided that for RINV (Feyer et al 2014). The available evidence from these clinical trials indicates that 5-hydroxytryptamine (5-HT3) receptor antagonists are the most active agents that have been

evaluated in randomized trials. However, other agents also may have a role in some settings (Feyer et al 2015).

Natural history of the indicated condition in the target population, including mortality and morbidity

Uncontrolled RINV negatively impacts patients' quality of life and can lead to patients delaying or refusing further radiotherapy, thereby compromising their treatment plan (Feyer et al 2011).

Important co-morbidities found in the target population

The simultaneous presence of cancer and other medical conditions (comorbidity) is frequent, especially in those aged ≥ 60 years (Coebergh et al 1999). For patients with serious comorbidity, the standard oncologic treatment may be altered because of an increased risk of complications or a limited life expectancy for non-oncologic reasons. The alternative treatment is usually radiotherapy (e.g. in patients with localized prostate cancer), but there are no studies that systematically assess frequency of different comorbidities in cancer patients receiving radiotherapy.

A retrospective Dutch study including 33369 cancer patients diagnosed with lung, rectal, breast, or prostate cancer or non-Hodgkin lymphoma in 1995 to 2002, shows that prevalence of comorbidity is greater in older age. Table 2-3 summarizes age group specific prevalence (%) of comorbidity in selected cancer patient's eligible for radiotherapy (Vulto et al 2006).

Table 2-3 Age specific prevalence of the most serious concomitant diseases among newly diagnosed cancer patients amenable to radiotherapy in South Netherlands

	Any comorbidity (%)			Heart and vascular disease (%)			COPD (%)			Hypertension (%)			Diabetes Mellitus (%)		
Tumor type	**Age 50-64**	**Age 65-79**	**Age >80**	**Age 50-64**	**Age 65-79**	**Age >80**	**Age 50-64**	**Age 65-79**	**Age >80**	**Age 50-64**	**Age 65-79**	**Age >80**	**Age 50-64**	**Age 65-79**	**Age >80**
Lung															
Male	53	74	72	18	34	32	20	24	31	11	15	11	7	10	11
Female	49	67	61	11	22	25	21	24	16	12	21	12	6	12	11
Colorectal															
Male	40	64	71	13	28	32	6	15	15	16	21	15	7	10	13
Female	37	56	65	5	14	24	5	8	9	15	25	25	5	14	17
Prostate	36	56	59	12	24	27	5	12	15	12	17	12	4	8	9
Breast	28	52	67	4	12	22	4	6	8	13	29	27	5	13	16
Non-Hodgkin Lymphoma															
Male	39	67	76	13	27	39	4	15	11	13	17	16	5	9	11
Female	32	61	65	5	11	23	2	8	4	14	26	20	6	12	13

Source: Vulto et al 2006
(Data from Eindhoven Cancer Registry, 1995-2002)

2.3 Indication: Postoperative Nausea and Vomiting

Incidence and prevalence

In a study published in 2008, the worldwide number of surgeries was estimated at 234.2 million (95% CI, 187.2-281.2) major surgeries per year, with approximately 32 million surgeries in France, Germany, Spain, Italy and United Kingdom (Weiser et al 2008). In this study, major surgery was defined as any intervention occurring in a hospital operating theatre usually requiring regional or general anesthesia or sedation. Postoperative nausea and vomiting is the most frequent side effect after anesthesia, occurring in an estimated 30% of patients overall during the 24 hours after emergence from anesthesia (Gan 2006, Franck et al 2010). The incidence reported in the literature does however vary depending on patient population and the underlying occurrence of risk factors. In high-risk populations, incidences of up to 70-85% have been reported (Gan 2006). Also, the number of risk factors can affect the estimated incidence. In a study by Apfel et al (1991), it was found that if none, 1, 2, 3 or 4 risk factors were present, the incidences of PONV were 10%, 21%, 39%, 61% and 78%, respectively. Lower incidence of 7.8% has also been reported from studies observing patients for only 3 hours after emergence from anesthesia (Junger et al 2001).

Demographics of the target population – age, gender, racial and/or ethnic origin

Among patients enrolled in four prospective, observational studies of PONV in Europe, the median or mean age of participants ranged from 42-52 years and the proportion of participants who were female ranged from 43-71% (Apfel et al 1991, Junger et al 2001, Apfel et al 2002, Franck et al 2010).

Risk factors for the disease

There are several well-established risk factors for PONV that are either patient-related, surgery-related or anesthesia-related. The patient-related risk factors are female gender from puberty (no gender difference has been seen in prepubescent patients), non-smoking status, history of PONV or motion sickness, childhood after infancy, and younger adulthood (children have twice the vomiting incidence as adults). Although many surgery sub-types have been investigated as risk factors for PONV, the only well-established surgery-related risk factor is increasing duration of surgical procedure. Anesthesia related risk factors include volatile nitrous oxide, balanced inhaled versus total IV anesthesia, high-dose neostigmine, and intraoperative or postoperative opioids (Gan 2006).

The main existing treatment options

The different classes of antiemetic agents commonly used for PONV include anticholinergics, antihistamines, phenothiazines, sedatives/anxiolytics, butyrophenones, dopamine antagonists, serotonin receptor antagonists, and corticosteroids, alone or in combination (Cruthirds et al 2013).

Natural history of the indicated condition in the target population, including mortality and morbidity

Although PONV is almost always self-limiting and non-fatal, it can cause significant morbidity, including dehydration, electrolyte imbalance, suture tension and dehiscence, venous hypertension and bleeding, esophageal rupture, and life-threatening airway compromise; however, the more severe complications are rare (Gan 2006).

Important co-morbidities found in the target population

There are no data available describing the occurrence of co-morbidities in the general population undergoing surgery. This population would represent patients with a wide range of underlying cause for the surgery as well as related co-morbidities. However, among the anesthesia-related adverse events, cardiac arrest and coma are of most concern since they can often lead to death. The current prevalence of anesthesia related cardiac arrests is between 0.8 and 3.3/10000 anesthetics administered and the prevalence of anesthesia-related brain injuries is between 0.15 and 0.9/10000 anesthetics administered (Haller et al 2011). Neurological complications such as paraplegia secondary to spinal or epidural anesthesia occur at rates of 0.6-0.9 per 100000 patients, and lower extremity neuropathies are identified in 1.5% of patients (Haller et al 2011). Complications associated with office-based anesthesia include vomiting during induction (0.1%) or in the recovery room (0.3%), laryngospasm or bronchospasm (0.3%), cardiac arrhythmias (0.1%), syncope (0.1%), prolonged recovery (0.2%), and peripheral vascular injury (0.1%) (Cruthirds et al 2013).

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

The content of this module has been omitted due to the mature nature of the product and extensive clinical safety experience.

4 Part II Safety specification Module SIII Clinical trial exposure

The content of this module has been omitted in accordance with GVP Module V:

- The product was placed on the market 10 or more years before the requirement for an RMP is established and
- The requirement for an RMP is not due to an application for a significant change to an existing marketing authorization.

5 Part II Safety specification Module SIV: Populations not studied in clinical trials

The content of this module has been omitted in accordance with GVP Module V:

- The product was placed on the market 10 or more years before the requirement for an RMP is established and
- The requirement for an RMP is not due to an application for a significant change to an existing marketing authorization.

6 Part II Safety specification Module SV: Post-authorization experience

Novartis:

Ondansetron has a well-characterized safety profile, supported by more than 30 years on the market for the management of CINV/RINV and PONV and a large cumulative post-marketing patient exposure. Novartis acquired ondansetron from GSK in Mar-2015 and the clinical development/ studies were performed by GSK. Data is not available to provide cumulative exposure or patient characteristics for participants in Clinical Trials (CTs). There are no ongoing or completed Novartis-sponsored clinical trials of ondansetron, thus, only post-marketing cumulative exposure data are provided.

Sandoz:

Approximately [redacted] healthy subjects have been exposed to ondansetron in Sandoz-sponsored bioequivalence and bioavailability studies cumulatively.

Additionally, [redacted] subjects were exposed to ondansetron in post-marketing studies performed cumulatively.

Data is not available to provide cumulative subject characteristics for participants in CTs for this product since International Birth Date (IBD) due to the maturity of this product.

6.1 Part II Module SV.1. Post-authorization exposure

The cumulative post-marketing exposure since the first launch of the product up to the data cut-off date of Ondansetron PSUR (01-Mar-2018 – 28-Feb-2021) is estimated to be [redacted] patient treatment years (PTY).

6.1.1 Part II Module SV.1.1 Method used to calculate exposure

An estimate of patient exposure is calculated based on worldwide sales volume in milligrams (mg) of ondansetron active substance through PSUR with DLP of 28-Feb-2021 and the Defined Daily Dose (DDD) of 16 mg.

Estimated exposure (PTY [for Novartis, Sandoz, and Pharmathen S.A]) = Amount sold in mg / (DDD*365).

The cumulative exposure broken down by route of administration and geographical region are presented in Table 6-1 and Table 6-2, respectively.

6.1.2 Part II Module SV.1.2. Exposure

Table 6-1 Cumulative exposure from marketing experience estimated using route of administration

Route of Administration	Exposure (patient treatment years [PTY])*
Suppositories	[redacted]
Tablet	
Injection	
Syrup	
Total	
GSK##	
Grand Total PTY	

*Cumulative exposure data available through 28 Feb 2021
##Formulation wise exposure including total amount sold wasn't available for GSK. The cumulative estimated exposure (PTY) has been taken from previous PSUR (Periodic Safety Update Report) as the product was transferred from GSK to Novartis in 2015.

Table 6-2 Cumulative exposure from marketing experience by country

Formulation	EEA*	US and Canada	Japan	ROW	Total
Suppositories	[redacted]				
Tablet					
Injection					
Syrup					
Total					
GSK PTY					
Grand Total					

*Including sales from Switzerland.
EEA: European Economic Area; GSK: GlaxoSmithKline; PSUR: Periodic Safety Update Report, PTY: Patient Treatment Years; ROW: Rest of the World; US: United States of America.

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

7.1 Potential for misuse for illegal purposes

There is no evidence that ondansetron has the potential for inducing misuse for illegal purposes.

8 Part II Safety specification Module SVII: Identified and potential risks

8.1 Part II Module SVII.1. Identification of safety concerns in the initial RMP submission

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

This section is not applicable as the RMP was already approved.

8.1.2 Part II Module SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

This section is not applicable as the RMP was already approved.

8.2 Part II Module SVII.2: New safety concerns and reclassification with a submission of an updated RMP

Based on GVP Module V (Revision 2) definition of important identified risks and important potential risks, following risks are no longer classified as important; therefore, the risks mentioned below are removed from the list of safety concerns.

- **Important identified risks:**
  - Profound hypotension and loss of consciousness when administered with apomorphine hydrochloride
  - Hypersensitivity
  - QT interval prolongation and Torsade de Pointes
  - Toxic skin eruption, including Toxic Epidermal Necrolysis
- **Important potential risks:**
  - Serotonin syndrome
  - Reduced clearance and prolonged half-life in patients with hepatic impairment
  - Sub-acute intestinal obstruction in patients with impaired gastrointestinal motility
  - Adverse events in breast-fed infants due to use of ondansetron during lactation
- **Missing information:**
  - Safety in pregnant women

There are no additional pharmacovigilance (PhV) activities and no additional risk minimization measures. Product information on clinical actions mentioned in the label to mitigate these risks are well established in the clinical practice. The missing information – “Safety in pregnant women” is proposed for removal since the important potential risk – “Adverse birth outcomes following use during pregnancy” is under evaluation and the CDS pregnancy section is updated with risk of orofacial cleft; therefore, safety in pregnant women is no longer considered to be missing information.

Post-marketing experience (safety database, literature review, and routine signal detection) of over 30 years has demonstrated the well-established safety profile for the product. These risks

are appropriately communicated through current labeling. The current routine risk minimization activities are found to be adequate to mitigate these risks.

The risks are being continued to monitor in the PSUR and the decision to continue will be taken based on data availability.

8.3 Part II Module SVII.3: Details of important identified risks, important potential risks, and missing information

The Medical Dictionary for Regulatory Activities (MedDRA) search terms included in Annex 1 is used for PhV of Adverse event (AE) and Serious Adverse Event (SAE) data originating from solicited and unsolicited reports and for the EudraVigilance interface. The MedDRA version 18.1 was used for the analysis of Adverse Drug Reactions (ADRs)/AEs.

8.3.1 Part II Module SVII.3.1. Presentation of important identified risks and important potential risks

8.3.1.1 Important Identified Risk: None

8.3.1.2 Important Potential Risk: Adverse birth outcomes following use during pregnancy

Table 8-1 Important potential risk – Adverse birth outcomes following use during pregnancy: Other details

Name of the risk	Details
Potential mechanisms	A number of factors influence pharmacology during pregnancies, such as a lengthened period of intestinal transfer, increased cardiac output, increased glomerular filtration rate and altered composition of plasma sex hormones. However, very little is known about the effects of these variables on drugs that are necessary for the health and well-being of pregnant women and placental transfer to a fetus (National Institution of Health 2014).
Evidence sources and strength of evidence	Literature and post-marketing reports (Rynn et al 2008, National Institution of Health 2014). Major birth defects occur in 2-4% of the general population in the US and Europe (Rynn et al 2008, Morris et al 2018).
Characterization of the risk	A cumulative review of literature (including published epidemiological studies), post-marketing reports and non-clinical data (cut off: 15-Oct-2015) was performed. The available data content neither confirm nor refute an increased risk of major birth defects including cardiac septal defects associated with the use of ondansetron during pregnancy. There is no consistent or compelling evidence from other sources indicating that exposure to ondansetron in early pregnancy causes major birth defects, including congenital cardiac defects. In human epidemiological studies, an increase in orofacial clefts was observed in infants of women administered ondansetron during the first trimester of pregnancy, the use of ondansetron in pregnancy is not recommended (Parker et al 2010).
Risk factors and risk groups	Use of ondansetron for nausea and vomiting of pregnancy or hyperemesis gravidarum during pregnancy (off-label use). Use of ondansetron for approved indications during pregnancy.
Preventability	The safety of ondansetron for use during pregnancy has not been established. The use of ondansetron during pregnancy is not recommended.
Impact on the benefit-risk balance of the product	Variable

Name of the risk	Details
Public health impact	The potential public health impact is considered low.

8.3.2 Part II Module SVII.3.2. Presentation of the missing information

None

9 Part II Safety specification Module SVIII: Summary of the safety concerns

Table 9-1 Table Part II SVIII.1: Summary of safety concerns

Important identified risk	None
Important potential risk	Adverse birth outcomes following use during pregnancy
Missing information	None

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

10.1 Part III.1. Routine pharmacovigilance activities

10.1.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection

No specific adverse reaction follow-up questionnaires were proposed for the risk in the program.

Other forms of routine pharmacovigilance activities for risks

No other forms of routine PhV activities for risk were proposed.

10.2 Part III.2. Additional pharmacovigilance activities

None

10.3 Part III.3 Summary Table of additional pharmacovigilance activities

No additional PhV activities are currently ongoing in the development program.

Table 10-1 Part III.1: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 – Required additional pharmacovigilance activities				
None				

11 Part IV: Plans for post-authorization efficacy studies

There are no plans for additional efficacy studies for ondansetron, which has been marketed since 1990. The efficacy profile of the product is applicable for the target populations.

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

Ondansetron is a nationally registered product in the EU; therefore, local differences between nationally approved Summary of product characteristics may exist.

Risk Minimization Plan

12.1 Part V.1. Routine risk minimization measures

Table 12-1 Table Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities:
Important identified risk	
None	
Important potential risk	
Adverse birth outcomes following use during pregnancy	**Routine risk communication:** This risk is appropriately communicated through current labeling. **Routine risk minimization activities recommending specific clinical measures to address the risk:** The use of ondansetron in pregnancy is not recommended. It is recommended that mothers receiving ondansetron should not breast-feed their babies. Pregnancy status should be verified for females of reproductive potential prior to starting the treatment with ondansetron. Females of reproductive potential should be advised that it is possible that ondansetron can cause harm to the developing fetus. Sexually active females of reproductive potential are recommended to use effective contraception (methods that result in less than 1 % pregnancy rates) when using ondansetron during the treatment and for two days after stopping treatment with ondansetron. Information present in section, 'Pregnancy and lactation'. **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine
Missing information	
None	

12.2 Part V.2. Additional Risk minimization measures

No additional risk minimization measures are proposed. Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

12.3 Part V.3. Summary of risk minimization measures

Table 12-2 Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risk		
None		
Important potential risk		
Adverse birth outcomes following use during pregnancy	**Routine risk minimization measures:** The use of ondansetron in pregnancy is not recommended. It is recommended that mothers receiving ondansetron should not breast-feed their babies. Pregnancy status should be verified for females of reproductive potential prior to starting the treatment with ondansetron. Females of reproductive potential should be advised that it is possible that ondansetron can cause harm to the developing fetus. Sexually active females of reproductive potential are recommended to use effective contraception (methods that result in less than 1 % pregnancy rates) when using ondansetron during the treatment and for two days after stopping treatment with ondansetron. Information present in section, 'Pregnancy and lactation'. Legal status: Prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Missing information		
None		

13 Part VI: Summary of the risk management plan for Zofran™ (ondansetron)

This is a summary of the RMP for Zofran™. The RMP details important risks of Zofran, how these risks can be minimized and how more information will be obtained about Zofran's risks and uncertainties (missing information).

Zofran's Product information give essential information to health care professionals and patients on how Zofran should be used.

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

13.1 Part VI: I. The medicine and what it is used for

Zofran is authorized for the management of chemotherapy- and radiotherapy-induced nausea and vomiting (CINV/RINV) and for the prevention of PONV (see Product information for the full indication). It contains ondansetron as the active substance, and it is given by oral, injectable, and rectal route.

13.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Zofran together with measures to minimize such risks and the proposed studies for learning more about Zofran's risks, are outlined below.

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

- Specific information, such as warnings, precautions, and advice on correct use, in the Product Information 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 minimize its risks.

Together, these measures constitute routine risk minimization measures.

13.2.1 Part VI: II.A: List of important risks and missing information

Important risks of Zofran are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered/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 Zofran. 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).

Table 13-1 List of important risks and missing information

Important identified risk	None
Important potential risk	Adverse birth outcomes following use during pregnancy
Missing information	None

13.2.2 Part VI: II.B: Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Table 13-2 Important identified risk

None

Table 13-3 Important potential risk: Adverse birth outcomes following use during pregnancy

Evidence for linking the risk to the medicine	Literature and post-marketing reports (Rynn et al 2008, National Institution of Health 2014). Major birth defects occur in 2-4% of the general population in the US and Europe (Rynn et al 2008, Morris et al 2018).
Risk factors and risk groups	Use of Zofran for nausea and vomiting of pregnancy or hyperemesis gravidarum during pregnancy (off-label use). Use of Zofran for approved indications during pregnancy.
Risk minimization measures	**Routine risk minimization measures** This risk is appropriately communicated through current labeling. The use of Zofran in pregnancy is not recommended. It is recommended that mothers receiving Zofran should not breast-feed their babies. Pregnancy status should be verified for females of reproductive potential prior to starting the treatment with Zofran. Females of reproductive potential should be advised that it is possible that Zofran can cause harm to the developing fetus. Sexually active females of reproductive potential are recommended to use effective contraception (methods that result in less than 1 % pregnancy rates) when using Zofran during the treatment and for two days after stopping treatment with Zofran. Information present in section, 'Pregnancy and lactation'. Legal status: Prescription only medicine. **Additional risk minimization measures** None

Table 13-4 Missing information

None

13.2.3 Part VI: II.C: Post-authorization development plan

13.2.3.1 II.C.1. Studies which are conditions of the marketing authorization

There are no studies which are conditions of the Marketing Authorization or specific obligation of Zofran.

13.2.3.2 II.C.2. Other studies in post-authorization development plan

There are no studies required for Zofran.

14 Part VII: Annexes

Annex 1 – EudraVigilance Interface

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study program

Table 14-1 Planned and ongoing studies

Study	Summary of objectives	Safety concerns addressed	Milestones
None			

Table 14-2 Completed studies

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission / Study report
A Randomized, Double-blind, Four-period Crossover Study to Investigate the Effect of Intravenous Ondansetron, a 5-HT3 Antagonist, on Cardiac Conduction as Compared to Placebo and Moxifloxacin in Healthy Adult Subjects Study S3A115458 Category 3	The primary objective was to characterize the effect of a single IV dose of 8 mg and 32 mg ondansetron (given over 15 minutes) on QT interval duration corrected for heart rate by Fridericia's formula (QTcF) as compared to placebo	QT interval prolongation (Thorough QT studies in healthy adults)	Date of LSLV: Dec 2011 Final CSR: 02-Jul-2012 [S3A115458]

Annex 3 - Protocols for proposed, ongoing and completed studies in the pharmacovigilance plan

Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this first or updated version of the RMP.

None

Part B: Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP.

None

Part C: Previously agreed protocols for ongoing studies and final protocols not reviewed by the competent authority.

None

Annex 4 - Specific adverse drug reaction follow-up forms

Targeted follow-up forms are not applicable.

Annex 5 - Protocols for proposed and ongoing studies in RMP part IV

Not applicable

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

No additional risk minimization activities have been proposed.

Annex 7 - Other supporting data (including referenced material)

Brief Statistical Description and Supportive Outputs

The Brief Statistical Description portion and Supportive Outputs of Annex 12 of RMP v 5.1 is presented separately.

For this RMP update no new statistical analysis was performed on data supporting the approved indications.

References List

External References

References are available on request.

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Novartis Internal References

[Ondansetron PSUR (01-Mar-2018 – 28-Feb-2021)]

Ondansetron Core Data Sheet Version 1.3 dated 10-Mar-2021

Annex 8 – Summary of changes to the risk management plan over time

Table 14-3 Summary of changes to the risk management plan over time

Version	Approval date	Change
1	18-Feb-2013	First RMP was a targeted RMP with one identified risk **Safety concerns** The following important identified risk was added: **Important identified risk**: QT interval prolongation and Torsade de Pointes **Important potential risk**: None **Missing information**: None **Pharmacovigilance Plan** None **Post-authorization efficacy plan** None **Risk minimization measures** None
2	29-Apr-2013	Revised version 1 in response to RMP Assessment Report **Safety concerns** No new safety concerns were added. **Important identified risk**: QT interval prolongation and Torsade de Pointes **Important potential risk**: None **Missing information**: None **Pharmacovigilance Plan** None **Post-authorization efficacy plan** None **Risk minimization measures** None
3	14-May-2013	Revised version 2 in response to comments from Medicines and Healthcare Products Regulatory Agency (MHRA) **Safety concerns** No new safety concerns were added. **Important identified risk**: QT interval prolongation and Torsade de Pointes **Important potential risk**: None **Missing information**: None **Pharmacovigilance Plan** None **Post-authorization efficacy plan** None **Risk minimization measures** None

Version	Approval date	Change
4	27-Apr-2015	Complete RMP prepared in response to request from Slovenia **Safety concerns** The following important identified and potential risks as well as missing information were added: **Important identified risk**: • Profound hypotension and loss of consciousness when administered with apomorphine hydrochloride • Hypersensitivity • Toxic epidermal necrolysis **Important potential risk**: • Serotonin syndrome • Adverse birth outcomes following use during pregnancy **Missing information**: Use during lactation **Pharmacovigilance Plan** None **Post-authorization efficacy plan** None **Risk minimization measures** None
5	11-Jun-2015	Changes made in response to comments from Slovenia regulatory authority **Safety concerns** The following important potential risks was added and missing information was updated: **Important identified risk**: None **Important potential risk**: • Reduced clearance and prolonged half-life in patients with hepatic impairment • Sub-acute intestinal obstruction in patients with impaired gastrointestinal motility • Adverse events in breast-fed infants due to use of ondansetron during lactation **Missing information**: • Safety in pregnant women **Pharmacovigilance Plan** None **Post-authorization efficacy plan** None **Risk minimization measures** None
5.1	18-Mar-2016	The already existing potential risk of serotonin syndrome is now delineated to also include serotonin syndrome following oral overdose of ondansetron in pediatric population **Safety concerns** No new safety concerns. **Important identified risk**: None **Important potential risk**: None

Version	Approval date	Change
		Missing information: None **Pharmacovigilance Plan** None **Post-authorization efficacy plan** None **Risk minimization measures** None
6		This RMP update is carried out in the new RMP template in accordance to the GVP Module V (Revision 2). **Safety concerns** The following important identified and potential risks as well as the missing information were removed: **Important identified risks**: • Profound hypotension and loss of consciousness when administered with apomorphine hydrochloride • Hypersensitivity • QT interval prolongation and Torsade de Pointes • Toxic skin eruption, including Toxic Epidermal Necrolysis **Important potential risks**: • Serotonin syndrome • Reduced clearance and prolonged half-life in patients with hepatic impairment • Sub-acute intestinal obstruction in patients with impaired gastrointestinal motility • Adverse events in breast-fed infants due to use of ondansetron during lactation **Missing information**: • Safety in pregnant women **Pharmacovigilance Plan** **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reactions follow-up checklists for – “Hypersensitivity including Anaphylaxis, QT interval prolongation or Torsades de Pointes, and Stevens-Johnson Syndrome /Toxic Epidermal Necrolysis” were removed. **Post-authorization efficacy plan** None **Risk minimization measures** None