PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

Important identified risk (s)	• Dose dependent QT interval prolongation including Torsade de pointes
Important potential risk (s)	None
Missing information	• Pregnancy and Lactation

VI.1.2 Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Not applicable.

VI.1.3 Summary of Post authorisation efficacy development plan

Not applicable.

VI.1.4 Summary table of risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important identified risk: Dose dependent QT interval	Accord product information (meant for prescribing physicians) for ondansetron includes following information on this	Currently available data does not support the need for additional risk minimization

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
prolongation including Torsade de pointes	safety concern: **Section 4.4:** Rarely, transient ECG changes including QT interval prolongation have been reported in patients receiving ondansetron. In addition, post-marketing cases of Torsade de Pointes have been reported in patients using ondansetron. Ondansetron should be administered with caution to patients who have or may develop prolongation of QTc. These conditions include patients with electrolyte abnormalities, with congenital long QT syndrome, or patients taking other medicinal products that lead to QT prolongation. Therefore, caution should be exercised in patients with cardiac rhythm or conduction disturbances, in patients treated with anti-arrhythmic agents or beta-adrenergic blocking agents and in patients with significant electrolyte disturbances. **Section 4.5:** Use of Ondansetron with QT prolonging drugs may result in additional QT	activities.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	prolongation. Concomitant use of Ondansetron with cardiotoxic drugs (e.g. anthracyclines) may increase the risk of arrhythmias **Section 4.8:** Cardiac disorders: Rare: Transitory changes in the electrocardiogram, including prolongation of the QT interval (including Torsade de Pointes) have been observed predominantly after intravenous administration of ondansetron.	
Missing information: Pregnancy and Lactation	Accord product information (meant for prescribing physicians) for ondansetron includes the following information: **Section 4.6:** The safety of ondansetron for use in human pregnancy has not been established. Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo, or fetus, the course of gestation and pre- and post-natal development. However as animal	Currently available data does not support the need for additional risk minimization activities.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	studies are not always predictive of human response the use of ondansetron in pregnancy is not recommended. If it is absolutely necessary that Ondansetron be given caution should be exercised when prescribing to pregnant women especially in the first trimester. A careful risk/benefit assessment should be performed. Tests have shown that ondansetron passes into the milk of lactating animals. It is therefore recommended that mothers receiving ondansetron should not breast-feed their babies. **Section 5.3:** Ondansetron and its metabolites accumulate in the milk of rats at a milk:plasma ratio of 5.2:1.	

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Ondansetron Injection contains the active ingredient ondansetron, which belongs to a group of medicines called anti-emetics.

Ondansetron Injection is used for

- Preventing nausea (feel sick) and vomiting (be sick) caused by

- chemotherapy for cancer in adults and in children aged ≥6 months.
- radiotherapy for cancer in adults

- Preventing and treatment of nausea and vomiting after surgery in adults and in children aged ≥ 1 month.

Nausea and vomiting caused by chemotherapy

Two of the most common side effects with medicines given to kill cancer cells are nausea and vomiting. These side effects have a significant impact on quality of life and can interfere with the cancer treatment. The frequency of nausea and vomiting is related to the drug or combination of drugs being administered for cancer treatment. Like 99% of the patients on Cisplatin cancer therapy experienced nausea if used without any nausea preventing drugs. Nausea and vomiting are mainly observed in child patients with cancer. Although both male and female are affected by vomiting and nausea with anti-cancer drugs however in some studies female patients experienced in more extent than male. Cancer drug-induced nausea and vomiting affects children of all ages; however, children younger than 6 years have been shown to have a lower occurrence than older children when receiving similar drugs.

Nausea and vomiting after surgery (postoperative)

The overall occurrence of nausea or vomiting after surgery is 1 in 5 and 1 in 3, respectively. Postoperative vomiting symptoms were not related to age in adults. Women had more often vomiting symptoms than men. Female gender, lengthy duration of medicine that keeps patients still during an operation (anaesthesia) and stomach and bone surgeries appeared to be most frequently associated with postoperative vomiting symptoms.

VI.2.2 Summary of treatment benefits

Ondansetron is recommended for use in chemotherapy-induced nausea and vomiting, radiotherapy induced nausea and vomiting and post operative nausea and vomiting.

A study was conducted in 415 patients aged 1 to 18 years. On the day of treatment with medicines given to kill cancer cells (chemotherapy), ondansetron is given through injection and after this it was given as syrup for 3 days. There was a complete control of vomiting. Another

study in 438 patients aged 1 to 17 years, 73% patient showed complete response. One more study was conducted in 75 children aged 6 to 48 months, 56% patient showed complete response.

A study was conducted in 670 children aged 1 to 24 months to control post-operative nausea and vomiting with ondansetron. Another study was conducted in 1469 male and female patients aged 2 to 12 years, to control post-operative nausea and vomiting with ondansetron. In both the studies, response with ondansetron was greater than no treatment (placebo).

However, Accord has not conducted any studies for ondansetron on expected benefit considering its similarity to the currently marketed product.

VI.2.3 Unknowns relating to treatment benefits

Information on the use of ondansetron in pregnant and breast feeding women is not available.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Dose dependent abnormal ECG including twisting in ECG spikes (Dose dependent QT interval prolongation including Torsade de pointes)	Abnormality in ECG was reported rarely. Twisting in ECG spikes was reported in post-marketing reports. This event is observed particularly in patients with ECG abnormality or patients taking other medicine which cause the ECG abnormality,	Yes Before starting the treatment, patients should inform their doctor for having any history of ECG abnormality, or taking any medicine to correct the same. During the treatment with ondansetron, patient should inform their doctor immediately for having any

		hearth problem.

Important potential risks

Risk	What is known
None	-

Missing information

Risk	What is known
Limited information on the drug use in pregnant and breast feeding mothers	The safety of ondansetron in human pregnancy has not been established. Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus. Tests have shown that ondansetron passes into the milk of lactating animals and hence, mothers receiving ondansetron should not breast-feed their babies.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

No studies planned.

VI.2.7 Summary of changes to the risk management plan over time

Version	Date	Safety Concern	Comment
2.0	17 October 2013	Following safety concerns are merged: **Important identified risk**: Dose dependent QT prolongation Torsade de pointes	-
3.0		There is no change in safety concerns.	RMP Part VI.2: Elements for a public summary is revised based on Risk Management Plan (RMP) Preliminary Assessment Report for Ondansetron 2 mg/ml Solution for Injection or Infusion (UK/H/1250/001/II/011), dated 17 September 2013.