PART VI: SUMMARY OF ACTIVITIES IN 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)	• Anaphylactic reactions • Urinary retention • Cardiac rhythm disorders • Glaucoma • Ileus
Important potential risk (s)	• Use during lactation
Important missing information	• Use in pregnancy

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.

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VI.1.4 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified risk: Anaphylactic reactions	Section 4.3, 4.4 and 4.8 of Solifenacin succinate film-coated tablets SmPC and corresponding sections of PIL have following information on this safety concern: **4.3 Contraindications** Hypersensitivity to the active substance(s) or to any of the excipients. **4.4 Special warnings and precautions for use** Anaphylactic reaction has been reported in some patients treated with solifenacin succinate. In patients who develop anaphylactic reactions, solifenacin succinate should be discontinued and appropriate therapy and/or measures should be taken. **4.8 Undesirable effects** Under Immune system disorders SOC, anaphylactic reaction reported with unknown frequency (cannot be estimated from the available data) from the post marketing data. Other routine risk minimisation measure including the prescription only status of the	Not proposed

	product.	
Important Identified risk: Urinary retention	Section 4.3, 4.4, 4.8 and 4.9 of Solifenacin succinate film-coated tablets SmPC and corresponding sections of PIL have following information on this safety concern: **4.3 Contraindications** Solifenacin is contraindicated in patients with urinary retention, severe gastrointestinal condition (including toxic megacolon), myasthenia gravis or narrow-angle glaucoma and in patients at risk for these conditions. **4.4 Special warnings and precautions for use** Solifenacin should be used with caution in patients with clinically significant bladder outflow obstruction at risk of urinary retention. **4.8 Undesirable effects** Under Renal and urinary disorders SOC, event urinary retention reported rarely (≥ 1/10,000 to <1/1,000) from the post marketing data. **4.9 Overdose** Overdosage with solifenacin succinate can potentially result in severe anticholinergic effects and as for other anticholinergics, symptoms urinary retention can be treated	Not proposed

	with catheterisation. Other routine risk minimisation measure including the prescription only status of the product.	
Important Identified risk: Cardiac rhythm disorders	Section 4.4, 4.8 and 4.9 of Solifenacin succinate film-coated tablets SmPC and corresponding sections of PIL have following information on this safety concern: **4.4 Special warnings and precautions for use** QT prolongation and Torsade de Pointes have been observed in patients with risk factors, such as pre-existing long QT syndrome and hypokalaemia. **4.8 Undesirable effects** Under Cardiac disorders SOC, events Torsade de Pointes, Electrocardiogram QT prolonged, Atrial fibrillation, Palpitations, Tachycardia reported with unknown frequency (cannot be estimated from the available data) from the post marketing data. **4.9 Overdose** Overdosage with solifenacin succinate can potentially result in severe anticholinergic effects and as for other anticholinergics, symptoms tachycardia can be treated with beta-blockers. As with other antimuscarinics, in case of	Not proposed

	overdosing, specific attention should be paid to patients with known risk for QT-prolongation (i.e. hypokalaemia, bradycardia and concurrent administration of medicinal products known to prolong QT-interval) and relevant pre-existing cardiac diseases (i.e. myocardial ischaemia, arrhythmia, congestive heart failure). Other routine risk minimisation measure including the prescription only status of the product.	
Important Identified risk: Glaucoma	Section 4.3 and 4.8 of Solifenacin succinate film-coated tablets SmPC and corresponding sections of PIL have following information on this safety concern: **4.3 Contraindications** Solifenacin is contraindicated in patients with urinary retention, severe gastrointestinal condition (including toxic megacolon), myasthenia gravis or narrow-angle glaucoma and in patients at risk for these conditions. **4.8 Undesirable effects** Under Eye disorders SOC, event glaucoma reported with unknown frequency (cannot be estimated from the available data) from the post marketing data Other routine risk minimisation measure including the prescription only status of the	Not proposed

	product.	
Important Identified risk: Ileus	Section 4.4 and 4.8 of Solifenacin succinate film-coated tablets SmPC and corresponding sections of PIL have following information on this safety concern: **4.4 Special warnings and precautions for use** Solifenacin should be used with caution in patients with gastrointestinal obstructive disorders. **4.8 Undesirable effects** Under Gastrointestinal disorders SOC, event ileus reported with unknown frequency (cannot be estimated from the available data) from the post marketing data. Other routine risk minimisation measure including the prescription only status of the product.	Not proposed
Important potential risk: Use during lactation	Section 4.6 and 5.3 of Solifenacin succinate film-coated tablets SmPC and corresponding sections of PIL have following information on this safety concern: **4.6 Fertility, pregnancy and lactation** Breast-feeding No data on the excretion of solifenacin in human milk are available. In mice, solifenacin	Not proposed

	and/or its metabolites was excreted in milk, and caused a dose dependent failure to thrive in neonatal mice. The use of solifenacin should therefore be avoided during breast-feeding. **5.3 Preclinical safety data** In the pre- and postnatal development study in mice, solifenacin treatment of the mother during lactation caused dose-dependent lower postpartum survival rate, decreased pup weight and slower physical development at clinically relevant levels. Other routine risk minimisation measure including the prescription only status of the product.	
Missing information: Use in Pregnancy	Section 4.6 and 5.3 of Solifenacin succinate film-coated tablets SmPC and corresponding sections of PIL have following information on this safety concern: **4.6 Fertility, pregnancy and lactation** Pregnancy No clinical data are available from women who became pregnant while taking solifenacin. Animal studies do not indicate direct harmful effects on fertility, embryonal/foetal development or parturition. The potential risk for humans is unknown. Caution should be exercised when prescribing	Not proposed

	to pregnant women. **5.3 Preclinical safety data** Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, fertility, embryofetal development, genotoxicity, and carcinogenic potential. Other routine risk minimisation measure including the prescription only status of the product.	

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

OAB (Overactive bladder) syndrome:

OAB is a common disorder that negatively affects the quality of life of patients and carries a large socioeconomic burden. OAB is a condition caused by sudden involuntary contraction (over activity) of the bladder detrusor muscles and is a problem with bladder-storage function that causes a sudden urge to urinate. The urge may be difficult to stop, and overactive bladder may lead to the involuntary loss of urine (incontinence). On the basis of a population-based survey of 16, 776 men and women aged 40 years and older selected from 6 countries France, Germany, Italy, Spain, Sweden and the United Kingdom, the prevalence of OAB in Europe has been estimated to be 15.6 and 17.4% for men and women respectively, with an overall prevalence of 16.6%. In the National Overactive Bladder Evaluation survey in which 11740 Americans agreed to participate, overall prevalence of OAB was 16.9% in women and 16.0% in men. Male gender, advanced age and obesity, are some of the common risk factors for OAB.

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VI.2.2 Summary of treatment benefits

Accord has not conducted any studies for solifenacin on expected benefit considering its similarity to the currently marketed product (Vesicare 5 mg and 10 mg film-coated tablets, Astellas Pharma Ltd) used for the treatment of the symptoms of overactive bladder syndrome, where the patient may find that he is unable to control urination that may need to rush to the toilet with no advance warning and/or go to the toilet frequently.

Treatment with solifenacin in doses of 5 mg and 10 mg daily was studied in several clinical trials in men and women with OAB. Both the 5 mg and 10 mg doses of solifenacin produced significant improvements. Efficacy was observed within one week of starting treatment and stabilised over a period of 12 weeks. After 12 weeks of treatment, approximately 50% of patients suffering from incontinence before treatment were free of incontinence episodes, and in addition 35% of patients achieved a micturition frequency of less than 8 micturitions per day. A long-term study demonstrated that efficacy was maintained for at least 12 months. Treatment of the symptoms of OAB also results in a benefit on a number of quality of life measures, such as general health perception, incontinence impact, role limitations, physical limitations, social limitations, emotions, symptom severity, severity measures and sleep/energy.

VI.2.3 Unknowns relating to treatment benefits

Not known

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Allergic reactions (Anaphylactic reactions)	There are chances of allergy to solifenacin succinate or any of the other ingredients of this medicine. Also possibilities of allergic attack or a severe skin reaction (e.g. blistering and	You must inform your doctor or pharmacist or discontinue your medicine immediately.

	peeling of the skin) with solifenacin succinate. Angioedema (skin allergy that results in the swelling that occurs in the tissue just below the surface of the skin) with airway obstruction (difficulty in breathing) has been reported in some patients on solifenacin succinate Patient may rarely develop allergic rash with solifenacin succinate.	
Accumulation of urine in the bladder (Urinary retention)	Risk of buildup of urine in the bladder due to inability to empty the bladder (urinary retention) with solifenacin succinate which is reported rarely. If patient have underlying condition then risk of accumulation of urine in the bladder is much higher. This is also one of the symptoms of overdose of solifenacin succinate.	Talk to your doctor or pharmacist before taking medicine or experienced difficulty passing the urine after taking solifenacin succinate.
(Cardiac rhythm disorders)	Risk of high levels of blood potassium which can cause abnormal heart rhythm like changes in the electrical activity of the heart (ECG), irregular heartbeat (Torsade de Pointes), feeling your heartbeat, faster heartbeat have been reported rarely.	You must inform your doctor or pharmacist immediately if you experience cardiac rhythm disorders.
Increased pressure in the eyes, with gradual loss of eye sight (Glaucoma)	Risk of increased pressure in the eyes, with gradual loss of eye sight reported with unknown frequency.	Before starting the treatment, inform to your doctor if you had glaucoma.

		Inform to your doctor of pharmacist if you experience glaucoma during the treatment with solifenacin.
Obstruction of the digestive system (Ileus)	Risk of developing constipation, nausea, indigestion with symptoms such as abdominal fullness, abdominal pain, burping, nausea, and heartburn (dyspepsia), stomach discomfort are common with solifenacin succinate. Lodging of a large amount of hardened stool in the large intestine (faecal impaction) also seen rarely.	Talk to your doctor or pharmacist before taking medicine if you had obstruction of the digestive system or if you experienced such condition after taking solifenacin succinate.

Important potential risks

Risk	**What is known**
Use during lactation	No data on the excretion of solifenacin in human milk are available. In mice, solifenacin and/or its metabolites was excreted in milk, and caused a dose dependent failure to thrive in neonatal mice. The use of solifenacin should therefore be avoided during breast-feeding.

Missing information

Risk	**What is known**
Limited	No clinical data are available from women who became pregnant while

information on the use in pregnant women	taking solifenacin. The potential risk for humans is unknown. Caution should be exercised when prescribing to pregnant women.

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 (if applicable)

No studies planned.

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

Version	Date	Safety concerns	Comment
4.0	22 September 2016	There were no changes in the safety concerns of this RMP.	This RMP (Section V.1, V.3 and VI.1.4) has been updated as per Preliminary Variation Assessment Report for Solifenacin Accord (DK/H/2339/001-002/IB/002**).**
3.0	30 June 2016	Following changes have been made in risks: *In Important identified risk:* Addition of • Anaphylactic reactions • Urinary retention • Cardiac rhythm disorders • Glaucoma • Ileus Deletion of "QT interval prolongation" *In Important potential risk:* Addition of "Use during lactation" Deletion of	As per the CMS Day 50 Comments from the FR for MRP procedure (DK/H/2339/001-002/E/001)

		• Angioedema with airway obstruction • Urinary retention in patients with significant bladder outlet obstruction • Worsening of effects in patients with gastrointestinal disorders *In Missing information:* Deletion of • Use of solifenacin in pediatric population • Effect of solifenacin on fertility of humans	

2.0	31 January 2014	Following risks were added: *Important identified risk:* QT interval prolongation *Important potential risk:* Urinary retention in patients with significant bladder outlet obstruction worsening of effects in patients with gastrointestinal disorders	Table VI.2.4 explained in layman language. RMP template updated as per "Guidance on format of the risk management plan (RMP) in the EU for Generics". EMA/465933/2013 Rev.1 Dated: 25 July 2013.