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VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Urinary incontinence (overactive bladder), or urine leakage in everyday language, is the uncontrolled and sudden loss of urine (urge incontinence). According to the mechanism of occurrence, several types of urinary incontinence are differentiated. The problem is common and increases with age. When you experience urinary incontinence, the urinary leakage is preceded by an urgent and uncontrollable need to urinate.

Urine is secreted by the kidneys and flows through two ducts (ureter) to the bladder. When the bladder is filled to a certain filling volume, the need for urination occurs. The urethral sphincter and the pelvic floor muscles contract to prevent leakage of urine. During urination, the sphincter voluntarily relaxes and the bladder muscles contract, allowing discharge of urine. Urination can be interrupted and controlled through the voluntary contraction of the urethral sphincter and the pelvic floor muscles.³

About 16.6% of the population over 40 years of age are reckoned to have overactive bladder.⁴

Solifenacin is indicated for the symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder syndrome.

VI.2.2 Summary of treatment benefits

Solifenacin belongs to the group of substances called anticholinergics. These medicines are used to reduce the activity of an overactive bladder. This enables patients to wait longer before having to go to the bathroom and increases the amount of urine that can be held by the bladder.¹

For patients who are motivated, non-drug therapy should be first line treatment. Where this treatment is not possible or fails, anticholinergic drugs must be considered.

In case of impossibility or failure, anticholinergic drugs may be considered.

Solifenacin has a similar efficacy to those of other current anticholinergic drugs in this indication.

VI.2.3 Unknowns relating to treatment benefits

None

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VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Anaphylactic reactions	<p>This medicine contains solifenacin and other ingredients including lactose and may cause serious allergic (anaphylactic) reactions, although not everybody gets them.</p> <p>Angioedema (swelling that occurs in the tissue just below the surface of the skin) with difficulty in breathing (airway obstruction) has been reported in some patients on solifenacin succinate.</p> <p>Allergic reactions reported with solifenacin are:</p> <ul style="list-style-type: none"> - Rare (may affect up to 1 in 1,000 people): itching (pruritus) and rash. - Very rare (may affect up to 1 in 10,000 people): allergic rash, skin allergy that results in the swelling that occurs in the tissue just below the surface of the skin (angioedema) and severe skin reaction (e.g. blistering and peeling of the skin). <p>Some serious allergic reactions such as exfoliative dermatitis and anaphylactic reaction are reported as side effects with a not known frequency (frequency cannot be estimated from the available data).</p>	<p>Solifenacin is contraindicated in patients who are allergic to solifenacin or any of the other ingredients of this medicine.</p> <p>If the patient experiences an allergic attack, or a severe skin reaction (e.g. blistering and peeling of the skin), he/she must inform his/her doctor or pharmacist immediately.</p> <p>If angioedema occurs, solifenacin should be discontinued immediately and appropriate therapy and/or measures should be taken.</p>
Inability to pass water or to empty the bladder completely (Urinary retention)	<p>An anticholinergic drug, as solifenacin, is a substance that prevents the action of a substance called acetylcholine.⁵ Acetylcholine is responsible for satisfactory bladder function.</p> <p>Risk of accumulation of urine in the bladder (urinary retention) is much higher in patients with trouble emptying their bladder (= bladder obstruction) or have difficulty in passing urine (e.g. a thin urine flow).</p> <p>Some urinary side effects reported with solifenacin are:</p> <ul style="list-style-type: none"> - Uncommon (may affect up to 1 in 	<p>Solifenacin 5 mg tablet and solifenacin 10 mg tablet are contraindicated in patients with the inability to pass water or empty bladder completely (urinary retention). Solifenacin should be used with caution in patients with trouble emptying their bladder (= bladder obstruction) or have difficulty in passing urine (e.g. a thin urine flow).</p> <p>The patients should inform their doctor if they are taking:</p>

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Risk	What is known	Preventability
	<p>100 people): difficulty in passing urine and</p> <ul style="list-style-type: none"> - Rare (may affect up to 1 in 1,000 people): build-up of urine in the bladder due to inability to empty the bladder (urinary retention). <p>Accumulation of urine in the bladder (urinary retention) could be one of the symptoms when the patients take more solifenacin than they should.</p>	<ul style="list-style-type: none"> - other anticholinergic medicines, effects and side effects of both medications can be enhanced. - cholinergics as they can reduce the effect of solifenacin. <p>If the patients have taken too much solifenacin or if a child has accidentally taken solifenacin, they should contact their doctor or pharmacist immediately.</p>
Cardiac rhythm disorders	<p>Electrocardiogram (ECG) is used to monitor the contraction of the heart (electrical activity of the heart). Solifenacin has been associated with prolongation of the QT interval on the ECG.</p> <p>In patients taking solifenacin with risk factors, such as pre-existing QT Syndrom and low potassium levels, QT prolongation and Torsades de Pointes have been observed.</p> <p>Some cardiac allergic reactions such as changes in the electrical activity of the heart (ECG QT prolonged), irregular heartbeat (atrial fibrillation), feeling the heartbeat (palpitations), faster heart beat reaction (tachycardia) are reported as side effects with a not known frequency (frequency cannot be estimated from the available data). Elevated heart rate (tachycardia) could be one of the symptoms when the patients take more solifenacin than they should.</p>	<p>If the patients have taken too much solifenacin or if a child has accidentally taken solifenacin, they should contact their doctor or pharmacist immediately.</p> <p>The patients should always consult their doctor, if they are considering stopping the treatment.</p>
Increased pressure in the eyes, with gradual loss of eye sight (glaucoma)	<p>Acetylcholine is responsible for satisfactory eye function. Some anticholinergic side effects reported with solifenacin are:</p> <ul style="list-style-type: none"> - Common (may affect up to 1 in 10 people): blurred vision. - Uncommon (may affect up to 1 in 100 people): dry (irritated) eyes. <p>Dilated pupils (mydriasis) could be one of the symptoms when the patients take more solifenacin than they should.</p>	<p>Solifenacin 5 mg tablet and solifenacin 10 mg tablet are contraindicated in patients suffer from increased pressure in the eyes, with gradual loss of eye sight (glaucoma).</p> <p>If the patients suffer from blurred vision, they should not drive or operate machinery. The patients should inform their doctor if they are taking:</p> <ul style="list-style-type: none"> - other anticholinergic medicines, effects and side effects of both medications can be

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Risk	What is known	Preventability
		<p>enhanced.</p> <ul style="list-style-type: none"> - cholinergics as they can reduce the effect of solifenacin. <p>If the patients have taken too much solifenacin or if a child has accidentally taken solifenacin, they should contact their doctor or pharmacist immediately.</p>
Potential worsening of effects in patients with bowel conditions (gastro-intestinal disorders) e.g. ileus	<p>Acetylcholine is responsible for satisfactory functioning of muscles and organs such as the bowel.</p> <p>Some anticholinergic side effects reported with solifenacin are:</p> <ul style="list-style-type: none"> - Very common (may affect up to 1 in 10 people): dry mouth. - Common (may affect up to 1 in 10 people): constipation. - Rare (may affect up to 1 in 1,000 people): lodging of a large amount of hardened stool in the large intestine (faecal impaction). <p>Ileus is reported as a side effect with a not known frequency (frequency cannot be estimated from the available data).</p>	<p>Solifenacin tablets are contraindicated in patients with severe stomach or bowel conditions (including toxic megacolon, a complication associated with ulcerative colitis).</p> <p>Solifenacin should be used with caution in patients with obstruction of the digestive system (constipation) or at risk of their digestive system slowing down (stomach and bowel movements).</p> <p>The patients should inform their doctor if they are taking:</p> <ul style="list-style-type: none"> - other anticholinergic medicines, effects and side effects of both medications can be enhanced. - cholinergics as they can reduce the effect of solifenacin. - medicines, like metoclopramide and cisapride, which make the digestive system work faster. Solifenacin can reduce their effect.
Reflux disease	<p>Reflux disease includes hiatus hernia and heartburn and can also occur in patients who are concurrently taking medicinal products (such as bisphosphonates) that can cause or worsen inflammation of the gullet (oesophagitis).</p> <p>Heartburn and stomach discomfort can be the consequence of an untreated reflux disease (gastro-oesophageal reflux).</p> <p>Side effects reported with solifenacin</p>	<p>Solifenacin should be used with caution in patients with a stomach tear or heartburn.</p>

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Risk	What is known	Preventability
	are: <ul style="list-style-type: none"> - Common (may affect up to 1 in 10 people): heartburn (dyspepsia). - Uncommon (may affect up to 1 in 100 people): gastro-oesophageal reflux. 	
Overdosage when used concomitantly with potent CYP3A4 inhibitors or in patients with moderate hepatic impairment or severe renal impairment	Solifenacin is mainly broken down in the body through CYP3A4 protein (enzyme). Simultaneous use of medicines that significantly inhibit (blocks) this enzyme may result in increased blood levels of solifenacin. These medicines, like ketoconazole, ritonavir, nelfinavir, itraconazole, verapamil and diltiazem decrease the rate at which solifenacin is broken down by the body. Solifenacin amounts in blood can increase in patients with severe kidney disease and in patients with moderate liver disease.	Solifenacin is contraindicated in patients suffering from severe kidney disease or moderate liver disease AND at the same time are being treated with medicines that may decrease the removal of solifenacin from the body (for example, ketoconazole). The doctor or pharmacist will have informed the patients if this is the case.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Use during lactation	No clinical data on the excretion of solifenacin in human milk are available. Studies performed in mice showed that solifenacin was detected in the milk and prevented their progeny from thriving. The patients should not use solifenacin if they are breast-feeding as solifenacin may get into their breast milk.

Missing information

Risk	What is known
Use during pregnancy	There are no data available on the effects of solifenacin in pregnant women. Animal studies do not show direct harmful effects on fertility or baby development. The patients should not use solifenacin if they are pregnant unless clearly necessary.
Effect of use in children	There are no data available on the effects of solifenacin in paediatric population. Solifenacin is contraindicated in children or adolescents under 18 years.

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

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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*

Not applicable

VI.2.7 *Summary of changes to the Risk Management Plan over time*

Version	Date	Safety Concerns	Comment
V 1.0	August 2015	<p><u>Important identified risks:</u> Use in patients with urinary retention, severe gastro-intestinal condition (including toxic megacolon), myasthenia gravis or narrow-angle glaucoma and in patients at risk for these conditions Hypersensitivity reactions Use in patients with severe renal impairment or moderate hepatic impairment who are on concomitant treatment with a potent CYP3A4 inhibitor</p> <p><u>Important potential risks:</u> Use in patients with severe renal impairment Use in patients with moderate hepatic impairment Interaction with potent CYP3A4 inhibitors Use in situations where hiatus hernia/gastro-oesophageal reflux and/or who are concurrently taking medicinal products can cause or exacerbate oesophagitis Use autonomic neuropathy Risk of QT prolongation and Torsade de Pointes</p> <p><u>Missing information:</u> Use in patients undergoing haemodialysis Use in patients with severe hepatic impairment Use in paediatric population Use in patients with neurogenic cause for detrusor overactivity Use during pregnancy and lactation, effects on fertility</p>	None
V 2.0	April 2016	<p><u>Important identified risks:</u> Use in patients with urinary retention, severe gastro-intestinal condition (including toxic megacolon), myasthenia gravis or narrow-angle glaucoma and in patients at risk for these conditions Hypersensitivity reactions Use in patients with severe renal</p>	Change of ATC code Change of EuQPPV name

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		<p>impairment or moderate hepatic impairment who are on concomitant treatment with a potent CYP3A4 inhibitor</p> <p><u>Important potential risks:</u></p> <p>Use in patients with severe renal impairment</p> <p>Use in patients with moderate hepatic impairment</p> <p>Interaction with potent CYP3A4 inhibitors</p> <p>Use in situations where hiatus hernia/gastro-oesophageal reflux and/or who are concurrently taking medicinal products can cause or exacerbate oesophagitis</p> <p>Use autonomic neuropathy</p> <p>Risk of QT prolongation and Torsade de Pointes</p> <p><u>Missing information:</u></p> <p>Use in patients undergoing haemodialysis</p> <p>Use in patients with severe hepatic impairment</p> <p>Use in paediatric population</p> <p>Use in patients with neurogenic cause for detrusor overactivity</p> <p>Use during pregnancy and lactation, effects on fertility</p>	
V 3.0	November 2016	<p><u>Important identified risks:</u></p> <p>Anaphylactic reactions</p> <p>Urinary retention</p> <p>Cardiac rhythm disorders</p> <p>Glaucoma</p> <p>Potential worsening of effects in patients with gastro-intestinal disorders e.g. ileus</p> <p>Reflux disease</p> <p>Overdosage when used concomitantly with potent CYP3A4 inhibitors or in patients with moderate hepatic impairment or severe renal impairment</p> <p><u>Important potential risks:</u></p> <p>Use during lactation</p> <p><u>Missing information:</u></p> <p>Use during pregnancy</p> <p>Effect of use in children</p>	All parts of the RMP have been updated accordingly.
V 4.0	April 2017	<p><u>Important identified risks:</u></p> <p>Anaphylactic reactions</p> <p>Urinary retention</p> <p>Cardiac rhythm disorders</p> <p>Glaucoma</p> <p>Potential worsening of effects in patients with gastro-intestinal disorders e.g. ileus</p> <p>Reflux disease</p> <p>Overdosage when used concomitantly with potent CYP3A4 inhibitors or in patients with moderate hepatic impairment or severe</p>	<p>The following parts have been modified as requested:</p> <ul style="list-style-type: none"> - Part I Product(s) Overview - Part VI.2.4 Summary of safety concerns - Part VI.2.7 Summary of changes to the Risk Management Plan over time - Annex 2

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		renal impairment <u>Important potential risks:</u> Use during lactation <u>Missing information:</u> Use during pregnancy Effect of use in children	