VI.2 Elements for a Public Summary

Overview of disease epidemiology

Overactive bladder

Overactive bladder (OAB) is a common condition which affects about one in six adults, men as well as women. OAB is not a normal part of aging, but with increasing age the risk of developing OAB increases.

Bladder filling and emptying is a complex interaction between kidneys, nerve signals and muscle activity. The kidneys produce urine, which is being stored in the bladder. As the bladder fills, nerve signals alert the brain and eventually cause the need to urinate. When urinating, nerve signals coordinate the relaxation of the pelvic floor muscles and the muscles of the urethra (urinary sphincter muscles). The muscles of the bladder tighten and push the urine out.

OAB is a condition which is defined by a set of symptoms. These symptoms occur because the muscles of the bladder are starting to contract involuntarily, creating the sensation of an urgent need to urinate. The urge (urinary urgency) may be difficult to stop, and overactive bladder may lead to the involuntary loss of urine (urinary incontinence). Other symptoms include frequent urination (urinary frequency; 8 or more times per day) and waking up two or more times in the night to urinate (nocturia).

Although OAB is not life-threatening it has a significant impact on quality of life, particularly emotional symptoms, sleep disturbance and interrupted sleep cycles, sexual health, work productivity and overall well-being, in severe cases leading to embarrassment and social withdrawal.

Neurogenic detrusor overactivity

Neurogenic detrusor overactivity (NDO) is a condition that occurs due to damage or malfunction of the nerves which control the bladder. NDO can result from a birth defect in the spinal cord, trauma of the spinal cord or a disease of the nervous system. NDO in children is usually the result of a birth defect of the spinal cord, e.g. in children with spina bifida (a birth defect where there is incomplete closing of the spinal cord and backbone of the

newborn child). The number of cases of NDO in children worldwide can vary. A study in Spain estimated the number to be 2.34 per 100,000 inhabitants per year.

NDO causes involuntary contractions of the bladder muscles that damage the bladder wall, leading to abnormally high pressures within the bladder as it fills with urine. These high pressures can reduce or stop the flow of urine in the tube (ureter) which connects the kidney to the bladder. This places the patient at high risk of developing a bladder or kidney infection. Irreversible damage to the kidneys can occur due to the direct effects of the high pressure within the ureter or as a result of frequent infections. Sudden increases in bladder pressure can also result in incontinence. Start of treatment early in life is important to protect the bladder and kidneys of NDO patients. NDO is typically treated by a combination of clean intermittent catheterization, which involves passing a small tube into the bladder to drain it on a regular basis, together with medication to decrease the contractile activity of the bladder.

Summary of treatment benefits

Solifenacin belongs to a group of medicines called antimuscarinics. It is used to treat the symptoms of a condition called OAB in adults and has been developed for the treatment of NDO in children aged two years and older.

Overactive bladder

The effect of solifenacin (received by 1811 patients) on the treatment of OAB symptoms was compared with the effect of placebo (1216 patients). Almost all patients were treated for 12 weeks, and had the possibility to continue treatment for up to 52 weeks. The effects of solifenacin could be seen after one week of treatment and were maintained over a period of 12 weeks. Studies examining the long-term use also showed that this effect was maintained for at least 12 months.

After 12 weeks of treatment almost half of the patients suffering from incontinence (involuntary urination) before treatment were free of incontinence episodes. Also, in about one third of the patients the frequency of urination dropped to less than eight urinations per day. The use of solifenacin to treat symptoms of OAB also improved the patient's quality of life. Patients reported a better quality of life in general as they were less bothered by the physical, social and emotional strains of their condition.

Neurogenic detrusor overactivity

The effect of solifenacin on patients with NDO was tested in 95 children and adolescents aged two years and older for up to 52 weeks. An improvement of the patient's bladder condition with solifenacin treatment was shown by a decrease in the number of involuntary contractions, a decrease in the pressure within the bladder during filling and a decrease in the number of incontinence episodes. An improvement was observed by 12 weeks of treatment and reached its maximum effect by 24 weeks. Studies examining the long-term use of solifenacin showed that this effect was maintained for at least 12 months.

Unknowns relating to treatment benefits

Solifenacin has not been studied in patients with severe liver disorder, in patients undergoing hemodialysis (filtering of the blood to remove harmful waste, extra salt and water when the kidneys have lost most of their ability to function), severe gastrointestinal conditions and myasthenia gravis (a rare condition that causes certain muscles to become weak) and should therefore not be used in these patients.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
QT prolongation	The QT interval is a measure of the electric activity in the heart which can be detected by an electrocardiogram (ECG). Torsade de Pointes is a variant of a fast heartbeat that can be a result of long QT interval. Some patients have in their medical or family history a long QT syndrome; low amounts of potassium (hypokalaemia) in the blood as well as some drugs can also cause a prolonged QT interval. A long QT syndrome is a heart rhythm disorder that can potentially cause fast, chaotic heartbeats. These rapid heartbeats may trigger a sudden fainting spell or cardiac arrest.	QT prolongation and Torsade de Pointes have been observed in patients with risk factors, such as pre-existing long QT syndrome and low amounts of potassium in their blood. Caution should be exercised when administering solifenacin in these patients.
Hypersensitivity reactions	Uncommonly, allergic reactions could occur with solifenacin. Hypersensitivity may present as sudden local swelling of the soft tissues of the body (e.g., the throat or tongue), difficult breathing and/or itching and rash (angioedema). The signs of allergic reactions can include skin rash (which can be itchy), hives (urticaria), and rarely swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing (angioedema). 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. If angioedema occurs, solifenacin should be discontinued immediately and appropriate therapy and/or measures should be taken.	Patients who are allergic to solifenacin or any of the other ingredients of this medicine should not use solifenacin. If patients experience an allergic attack, or a severe skin reaction (e.g., blistering and peeling of the skin), they must inform their doctor immediately, and stop using solifenacin.
Urinary Retention	The inability to pass urine or to empty the bladder completely may occur during treatment with solifenacin. Patients are at increased risk to experience urinary retention due to older age, the presence of concomitant diseases such as bladder outlet obstruction,	Solifenacin should not be taken by patients who have an inability to pass water or to empty their bladder completely (urinary retention). If any of side effects such as difficulty in passing urine or inability to empty the

Risk	What is known	Preventability
	benign prostatic hyperplasia, neurologic disorders, infections and others. Side effects of difficulty in passing urine have been reported uncommonly (1 in 100 people), and in rare cases (1 in 1,000 people) build-up of urine in the bladder due to inability to empty the bladder (urinary retention) have been reported. The standard treatment of patients with NDO is clean intermittent catheterization to manage problems due to high intravesical pressures, therefore the risk of urinary retention in these patients due to drug induced detrusor hypo-function is not considered likely.	bladder occur, solifenacin should be discontinued and appropriate therapy and/or measures should be taken.
Glaucoma	Glaucoma is a term that describes a group of eye conditions that affect vision. Glaucoma often affects both eyes, usually in varying degrees. One eye may develop glaucoma quicker than the other. Glaucoma occurs when the drainage tubes (trabecular meshwork) within the eye become slightly blocked. This prevents eye fluid (aqueous humor) from draining properly. When the fluid cannot drain properly, pressure builds up. This is called intraocular pressure. This can damage the optic nerve (which connects the eye to the brain) and the nerve fibers from the retina (the light-sensitive nerve tissue that lines the back of the eye). Increased pressure in the eyes has been reported as side effect with solifenacin but the frequency is not known because it cannot be estimated from the available data.	Patients who suffer from increased pressure in the eyes, with gradual loss of eye sight (glaucoma) should not be treated with solifenacin. Attending regular optician appointments will help to ensure any signs of glaucoma can be detected early and allow treatment to begin. Glaucoma can be treated with eye drops, laser treatment or surgery. However, early diagnosis is important because any damage to the eyes cannot be reversed. Treatment aims to control the condition and minimize future damage. If left untreated, glaucoma can cause visual impairment (sight loss that cannot be fully corrected using glasses or contact lenses). But if it is diagnosed and treated early enough, further damage to vision can be prevented.
Ileus	Ileus is temporary absence of the normal contractile movements of the bowel wall. Like an obstruction (blockage) of the intestines, ileus prevents the passage of intestinal contents. The symptoms of ileus are abdominal bloating, nausea, vomiting, severe constipation, loss of appetite, and cramps. Side effects of obstruction of the digestive system (constipation) have commonly been reported (1 in 100 people), lodging of a large amount of hardened stool in the large intestine (faecal impaction) has been reported rarely (1 in 1,000 people).	Patients at risk of their digestive system slowing down (stomach and bowel movements) or who have some obstruction of the digestive system (constipation) should inform their doctor before taking solifenacin.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
None	

Missing information

Risk	What is known
Use of solifenacin in children under the age of six months, either exposed to solifenacin directly or exposed via breast-feeding	In mice, solifenacin-related material was excreted in the breast milk. However, in humans, no such data regarding the excretion of solifenacin-related material in breast milk is available. In juvenile mice that were exposed to solifenacin from 10 days after birth, an increased death rate was observed in 16 to 41-day old mice. Whilst the primary cause of death is considered to be stress, associated with dosing and handling, an effect of solifenacin cannot be excluded. The timing of the deaths is consistent with the period of development of the cholinergic nervous system (a nervous system that uses a molecule called "acetylcholine" to send signals around the body) and the blood-brain-barrier (a protective layer between the blood and the brain) in mice. In humans these systems are considered to be fully mature at birth and 6 months of age respectively. Thus whilst the clinical implications of the findings in juvenile mice are not known, the risk to infants aged 6 months and above is considered to be low. The observed increased death rate in younger juvenile mice is also considered to be related to the higher exposures to solifenacin observed below 21 days of age. This is not considered a risk for children over 6 months of age as the doses to be used to achieve optimal therapeutic effect will be adjusted according to a physiological based pharmacokinetic model (a model predicting the way solifenacin is processed in the body of developing infants and children).
Use in pregnancy	There is limited clinical data available from women who became pregnant while taking solifenacin. Animal studies do not indicate direct harmful effects on fertility, embryonal / foetal development or child birth. The effects of solifenacin use during pregnancy in humans are unknown.

Summary of additional risk minimization 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 minimizing them. An abbreviated version of this in lay language is provided in the form of the Package Leaflet (PL). The publishing of these documents are known as routine risk minimization measures.

Planned post-authorization development plan

List of studies in post-authorization development plan

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
None				

Studies which are a condition of the marketing authorization

None

Summary of changes to the Risk Management Plan over time

Table 27 Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.0	01-OCT-2014	Important Identified risks "QTc prolongation/ Torsade de Pointes" "Urinary Retention" "Hypersensitivity reactions, including anaphylactic reaction and angioedema" "Glaucoma" "Ileus" Important potential risks: None Missing information: "Human relevance of increased frequency of unexplained death in juvenile mice"	Initial version of RMP
1.1	15-APR-2015	Missing information: The concern of "Human relevance of increased frequency of unexplained death in juvenile mice" was changed to "Use of solifenacin in infants and children either exposed to solifenacin directly or via breast-feeding" "Use in pregnancy" added as missing information.	Following EMA review: The concern regarding the unexplained death juvenile mice was rephrased. Also "Exposure during pregnancy" was added to list of missing information.
2.0	02-JUL-2015	No changes to the safety concerns	The results from the completed OAB studies in children were added to the RMP.
2.1	10-FEB-2017	Missing information: The concern of "Use of solifenacin in infants and children either exposed to solifenacin directly or via breast-feeding" was changed to "Use of solifenacin in children under the age of six months, either exposed to solifenacin directly or exposed via breast-feeding"	The results from the completed NDO studies in children were added to the RMP. As a consequence, the verbatim for missing information regarding exposure in children has been updated.
3.0	02-MAY-2017	Minor update to the epidemiology data for the safety concern of Ileus	Update of epidemiology data. Alignment with updated EU SmPC pertaining to proposed

Version	Date	Safety Concerns	Comment
			NDO indication.