

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Pain is one of the most common reasons for a patient to seek medical attention. Moderate or severe intensity pain can be acute or chronic. While acute pain is a normal sensation triggered in the nervous system to alert a possible injury, chronic pain is different. It persists for longer period of time. Pain signals keep firing in the nervous system for weeks, months or even years. There may have been an initial mishap – sprained back, serious infection, or there may be an on-going cause of pain – arthritis, cancer, ear infection, etc., but some people suffer with chronic pain in the absence of any past injury or evidence of body damage. Estimates suggest that 20 % of adults suffer from pain globally and 10 % are newly diagnosed with chronic pain each year. By any measure, pain is an enormous global health problem. A recent market research report indicates that more than 1.5 billion people worldwide suffer from chronic pain. It was also reported that approximately 49.7 million people in European Union reported pain by both its severity and frequency. Of these, 11.2 million reported severe pain, 29.4 million reported moderate pain and 9.0 million reported mild pain. Globally, it has been estimated that one in five adults suffers from pain and that another one in 10 adults is diagnosed with chronic pain each year. While pain affects all populations, regardless of age, sex, income, race/ethnicity or geography, it is not distributed equally across the globe. Those who experience pain can experience acute, chronic or intermittent pain, or a combination of the three.

VI.2.2 Summary of treatment benefits

Tramadol has an established place in the treatment of moderate to severe painful conditions. It has been used in post-surgical pain, obstetric pain, and chronic pain of mechanical and neurogenic origin. Initially, painful conditions are treated with non-opioids, e.g. paracetamol, thereafter, if the pain persists, mild opioids, e.g. codeine, and strong opioids, e.g. tramadol, are used in a stepwise manner.

Tramadol hydrochloride is an orally active, centrally acting analgesic with a dual mechanism of action. Unlike other opioids, tramadol has no clinically relevant effects on respiratory or cardiovascular parameters. Compared with NSAIDs, tramadol does not aggravate hypertension or congestive heart failure, nor does it have the potential to cause peptic ulcers. Tramadol may prove particularly useful in patients with poor cardiopulmonary function, including the elderly, the obese and smokers, in patients with impaired hepatic or renal function, and in patients in whom nonsteroidal anti-inflammatory drugs are not recommended or need to be used with caution.

Tramadol shows a selective interaction with mu receptors, which are responsible for nociception, and has weak pharmacodynamic activity on other opioid receptors. At the same time, it acts synergistically

1.8.2 clean	Tramadol hydrochloride
Risk Management System	capsules, hard

on neuroamine transmission by inhibiting synaptic noradrenaline (norepinephrine) reuptake and inducing intrasynaptic serotonin (5-hydroxytryptamine; 5-HT) release.

Tramadol has a dose-dependent analgesic efficacy that lies between that of codeine and morphine, with a parenteral potency comparable to that of pethidine, i.e. about 10 to 20 % of the gold standard morphine. Oral bioavailability is high (85 to 100 %) and permits easy conversion from the oral to the parenteral route and vice versa.

Unlike other opioids, tramadol is not usually associated with the development of tolerance, physical dependence or psychological addiction. Although tramadol can produce drug dependence of the mu-opioid type (like codeine or dextropropoxyphene) and potentially may be abused, there has been little evidence of abuse in foreign clinical experience. In clinical trials, tramadol produced effects similar to an opioid, and at supratherapeutic doses was recognized as an opioid in subjective/behavioral studies. Tolerance development has been reported to be relatively mild and withdrawal, when present, is not considered to be as severe as that produced by other opioids.

VI.2.3 Unknowns relating to treatment benefits

The tramadol has been in use for many years. Many studies have been performed and a lot of data have been obtained from the patients treated with this drug. The patients with special conditions, such as renal insufficiency, hepatic impairment, and elderly are considered to be well evaluated.

There is a lack of studies among pregnant women therefore the drug should not be used during pregnancy. Also, there is not enough safety data in children; however, injections 50 mg/1 ml, hard capsules 50 mg and prolonged-release tablets 100 mg, 150 mg, 200 mg, are not intended for children under age of 1, 12 and 14 years, respectively, and they should not be treated with it.

VI.2.4 Summary of safety concerns

Tramadol solution for injections 50 mg/1 ml, 100 mg/2 ml and Tramadol capsules hard 50 mg:

Important identified risks

Risk	What is known	Preventability
Convulsions (e.g. in patients with poorly controlled epilepsy)	<p>Adverse drug reaction listed in PIL.</p> <p><i>Epilepsy</i> is a brain disorder that causes people to have recurring seizures. The seizures happen when clusters of nerve cells, or neurons, in the brain send out the wrong signals. People may have strange sensations and emotions or behave strangely. They may have violent muscle spasms or lose consciousness.</p> <p>Seizures have occurred in</p>	<p>Routine pharmacovigilance is sufficient.</p> <p>By monitoring for early symptoms.</p> <p>The proposed PIL contains the following information:</p> <p>Tramadol should not be taken in cases of epilepsy that cannot be adequately controlled by treatment.</p> <p>Doctor or pharmacist should be informed if the patients are prone to epilepsy or seizures.</p>

RMS001320_2	12.12.2016 - Updated: 21.07.2017 - CONFIDENTIAL	Page 39 of 50
-------------	---	---------------

1.8.2 clean	Tramadol hydrochloride
Risk Management System	capsules, hard

	<p>people taking a normal tramadol dosage. However, they appear to be most common in people taking high doses, such as people who have a problem with tramadol abuse. Other people who may be at a high risk for seizures with tramadol include people who:</p> <ul style="list-style-type: none"> - have epilepsy - have had seizures in the past - have head trauma - are withdrawing ("detoxing") from drugs or alcohol - have a brain or spinal infection. <p>Medications can also increase the risk of seizures due to tramadol.</p>	<p>Epileptic seizures have been described in patients using tramadol at the recommended dose. The risk may be increased when the recommended maximum daily dose of 400 mg tramadol is exceeded.</p> <p>Doctor or pharmacist should also be informed, if the patients take medicines which may cause convulsions (epileptic seizures), such as certain antidepressants or antipsychotics. The risk of having a seizure may increase if tramadol is used at the same time. Doctor will decide whether tramadol is suitable for the patients.</p> <p>Like all medicines, this medicine can cause side effects, although not everybody gets them.</p>
Overdose	<p>Event listed in PIL.</p> <p>An <i>overdose</i> is the condition of taking a larger dose of a drug than the body is able to handle. Overdoses can occur accidentally or deliberately. Accidental overdoses are less common with prescription drugs, because the strength and dosage is known, and the physician provides instructions regarding the appropriate amount. However, accidental overdoses of prescription drugs can occur at times of confusion or forgetfulness, if the person has experienced extreme weight loss, or if he or she has discontinued or reduced the usual dose since the drug was originally prescribed.</p> <p>Symptoms of tramadol overdose can vary, but they can be extremely dangerous since</p>	<p>Routine pharmacovigilance is sufficient.</p> <p>By monitoring for early symptoms. The proposed PIL contains the following information:</p> <p>If patients have used an additional dose of tramadol by mistake, usually there will be no negative effects. The next dose of tramadol should be used as prescribed.</p> <p>If patients have used a dose significantly higher than the recommended one, the following may occur: narrow pupils, vomiting, blood pressure fall, rapid heartbeat, circulatory collapse, consciousness disturbances up to coma (deep unconsciousness), epileptic seizures and difficult breathing up to respiratory arrest. In case of these signs, doctor should be</p>

1.8.2 clean	Tramadol hydrochloride
Risk Management System	capsules, hard

	<p>this drug suppresses the central nervous system.</p>	<p>informed immediately.</p> <p>Like all medicines, this medicine can cause side effects, although not everybody gets them.</p>
<p>Dependence, withdrawal syndrome, tolerance, abuse</p>	<p>Event listed in PIL.</p> <p><i>Drug dependence</i> means that a person needs a drug to function normally. Abruptly stopping the drug leads to withdrawal symptoms. Drug addiction is the compulsive use of a substance, despite its negative or dangerous effects.</p> <p>A person may have a physical dependence on a substance without having an addiction. Some other drugs can cause addiction without leading to physical dependence.</p> <p><i>Withdrawal syndrome</i>, also called a discontinuation syndrome, occurs in drug and alcohol addicted individuals who discontinue or reduce the use of their drug of choice. The risk of a discontinuation syndrome occurring increases with dosage and length of use. The process of eliminating drugs and alcohol from the body is known as detoxification. Anxiety, insomnia, nausea, perspiration, body aches, and tremors are just a few of the physical and psychological symptoms of drug and alcohol withdrawal that may occur during detoxification.</p> <p>Long-term use of high doses of tramadol may be associated with <i>physical dependence</i> and a withdrawal syndrome. Some people may experience withdrawal symptoms when they stop taking tramadol. These may include feeling</p>	<p>Routine pharmacovigilance is sufficient.</p> <p>By monitoring for early symptoms.</p> <p>The proposed PIL contains the following information:</p> <p>If tramadol is taken over a long period of time dependence may occur, although the risk is very low. When treatment is stopped abruptly, signs of withdrawal may appear.</p> <p>With prolonged use, the effect of tramadol may subside and higher doses must be taken (development of tolerance). In patients with a tendency to drug abuse or drug dependence, treatment with tramadol should only be for short periods and under strict medical supervision.</p> <p>Like all medicines, this medicine can cause side effects, although not everybody gets them.</p>

1.8.2 clean	Tramadol hydrochloride
Risk Management System	capsules, hard

	<p>agitated, anxious, nervous or shaky, or having difficulty sleeping.</p> <p>When drugs are used repeatedly over time, <i>tolerance</i> may develop. Tolerance occurs when the person no longer responds to the drug in the way that person initially responded. Stated another way, it takes a higher dose of the drug to achieve the same level of response achieved initially. The development of tolerance is not addiction, although many drugs that produce tolerance also have addictive potential.</p> <p><i>Drug abuse</i> can lead to drug dependence or addiction. People who use drugs for pain relief may become dependent, although this is rare in those who don't have a history of addiction.</p> <p>Treatment with tramadol is not recommended in patients with a tendency to abuse drugs or a history of drug dependence, and in patients who are chronically using opioids.</p>	
Concomitant use with anticoagulants	<p>Event listed in PIL.</p> <p>Tramadol may increase anticoagulant effect of anticoagulant therapy.</p> <p>Caution should be exercised during concomitant treatment with tramadol and coumarin derivatives (e.g. warfarin) due to reports of increased INR (The international normalised ratio = INR is a laboratory measurement of how long it takes blood to form a clot. It is used to determine the effects of oral anticoagulants on the clotting system.) and ecchymoses (skin discoloration caused by the escape of blood</p>	<p>Routine pharmacovigilance is sufficient.</p> <p>By monitoring for early symptoms.</p> <p>The proposed PIL contains the following information:</p> <p>Taking coumarin anticoagulants (medicines for blood thinning), e.g. warfarin, together with tramadol may affect blood clotting and bleeding may occur.</p> <p>Like all medicines, this medicine can cause side effects, although not everybody gets them.</p>

1.8.2 clean	Tramadol hydrochloride
Risk Management System	capsules, hard

	into the tissues from ruptured blood vessels; ecchymoses can occur in mucous membranes, for example, in the mouth) in some patients.	
Serotonin syndrome during concomitant use with serotonergic drugs	<p>Event listed in PIL.</p> <p><u>Serotonin syndrome</u> occurs when the body has too much serotonin, a chemical found in the nervous system. Serotonin syndrome symptoms may include restlessness, hallucinations, loss of coordination, fast heartbeat, rapid changes in blood pressure, increased body temperature, overactive reflexes, nausea, vomiting, and diarrhea.</p> <p>Patients should be informed that tramadol may cause seizures and/or serotonin syndrome with concomitant use of serotonergic agents (including SSRIs, SNRIs, and triptans) or drugs that significantly reduce the metabolic clearance of tramadol.</p> <p>If concomitant treatment of tramadol with a drug affecting the serotonergic neurotransmitter system is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.</p>	<p>Routine pharmacovigilance is sufficient.</p> <p>By monitoring for early symptoms.</p> <p>Patients should be informed that tramadol may cause seizures and/or serotonin syndrome with concomitant use of serotonergic agents (including SSRIs, SNRIs, and triptans) or drugs that significantly reduce the metabolic clearance of tramadol.</p> <p>If concomitant treatment of tramadol with a drug affecting the serotonergic neurotransmitter system is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.</p> <p>Like all medicines, this medicine can cause side effects, although not everybody gets them.</p>
Concomitant use with CNS depressants	<p>Event listed in PIL.</p> <p><u>CNS depressants</u>, sometimes referred to as sedatives and tranquilizers, are substances that can slow brain activity. This property makes them useful for treating anxiety and sleep disorders.</p> <p>Risk of central nervous system and respiratory depression may be increased with the concomitant use of tramadol.</p>	<p>Routine pharmacovigilance is sufficient.</p> <p>By monitoring for early symptoms.</p> <p>The proposed PIL contains the following information:</p> <p>Doctor or pharmacist should also be informed, if the patients take tramadol at the same time as medicines that also have a depressant effect on brain function. Patients may feel dizzy or faint. If this happens,</p>

1.8.2 clean	Tramadol hydrochloride
Risk Management System	capsules, hard

	<p>Patients have to use tramadol with caution and in reduced dosages. Patients also have to avoid alcohol.</p>	<p>doctor should be informed. The other medicines include sedatives, sleeping pills and certain painkillers, such as morphine and codeine (also as a cough suppressant), and alcohol.</p> <p>Like all medicines, this medicine can cause side effects, although not everybody gets them.</p>
--	--	--

Important potential risks

Risk	What is known
Use in patients with a tendency of prolonged elimination (elderly above over 75 years or hepatic/renal impairment)	In elderly patients (above 75 years) the excretion of tramadol may be delayed. Doctor may recommend prolonging the dosage interval.
Use during pregnancy and breast-feeding	<p>There is only little information regarding the safety of tramadol during pregnancy. Therefore, tramadol should not be used in cases if the women are or could be pregnant. Chronic use of tramadol during pregnancy can lead to habituation of the unborn child to tramadol and consequently to withdrawal symptoms after birth in the newborn.</p> <p>Generally, the use of tramadol is not recommended during breast-feeding. Very small amounts of tramadol are excreted into breast milk. On a single dose it is usually not necessary to interrupt breast feeding.</p>

Missing information

Risk	What is known
<p>Tramadol solution for injections 50 mg/1 ml, 100 mg/2 ml only:</p> <ul style="list-style-type: none"> Use in paediatric population under 1 year of age <p>Tramadol capsules hard 50 mg only:</p> <ul style="list-style-type: none"> Use in paediatric population under 12 years of age 	<p>Tramadol solution for injections 50 mg/1 ml and 100 mg/2 ml only:</p> <p>Tramadol is not intended for use in children under 1 year of age</p> <p>Tramadol capsules hard 50 mg only:</p> <p>Tramadol is not intended for use in children under 12 years of age</p>

Tramadol hydrochloride prolonged-release tablets 100 mg, 150 mg, 200 mg:

RMS001320_2	12.12.2016 - Updated: 21.07.2017 - CONFIDENTIAL	Page 44 of 50
-------------	---	---------------

1.8.2 clean	Tramadol hydrochloride
Risk Management System	capsules, hard

Important identified risks

Risk	What is known	Preventability
Convulsions (e.g. in patients with poorly controlled epilepsy)	<p>Adverse drug reaction listed in PIL.</p> <p><i>Epilepsy</i> is a brain disorder that causes people to have recurring seizures. The seizures happen when clusters of nerve cells, or neurons, in the brain send out the wrong signals. People may have strange sensations and emotions or behave strangely. They may have violent muscle spasms or lose consciousness.</p> <p>Seizures have occurred in people taking a normal tramadol dosage. However, they appear to be most common in people taking high doses, such as people who have a problem with tramadol abuse. Other people who may be at a high risk for seizures with tramadol include people who:</p> <ul style="list-style-type: none"> - have epilepsy - have had seizures in the past - have head trauma - are withdrawing ("detoxing") from drugs or alcohol - have a brain or spinal infection. <p>Medications can also increase the risk of seizures due to tramadol.</p>	<p>Routine pharmacovigilance is sufficient.</p> <p>By monitoring for early symptoms.</p> <p>The proposed PIL contains the following information:</p> <p>Doctor or pharmacist should be informed if the patients have periodic epileptic seizures.</p> <p>Epileptic seizures have been described in patients using tramadol at the recommended dose. The risk may be increased when the recommended maximum daily dose of 400 mg tramadol is exceeded.</p> <p>Doctor or pharmacist should also be informed, if the patients take medicines which may cause convulsions (epileptic seizures), such as certain antidepressants or antipsychotics. The risk of having a seizure may increase if tramadol is used at the same time. Doctor will decide whether tramadol is suitable for the patients.</p> <p>Like all medicines, this medicine can cause side effects, although not everybody gets them.</p>
Overdose	<p>Event listed in PIL.</p> <p>An <i>overdose</i> is the condition of taking a larger dose of a drug than the body is able to handle. Overdoses can occur accidentally or deliberately. Accidental overdoses are less common with prescription drugs, because the strength and dosage is known, and the physician provides instructions</p>	<p>Routine pharmacovigilance is sufficient.</p> <p>By monitoring for early symptoms.</p> <p>The proposed PIL contains the following information:</p> <p>If patients have used an additional dose of tramadol by mistake, usually there will be no negative effects. The next dose of tramadol should be used</p>

RMS001320_2	12.12.2016 - Updated: 21.07.2017 - CONFIDENTIAL	Page 45 of 50
-------------	---	---------------

1.8.2 clean	Tramadol hydrochloride
Risk Management System	capsules, hard

	<p>regarding the appropriate amount. However, accidental overdoses of prescription drugs can occur at times of confusion or forgetfulness, if the person has experienced extreme weight loss, or if he or she has discontinued or reduced the usual dose since the drug was originally prescribed.</p> <p>Symptoms of tramadol overdose can vary, but they can be extremely dangerous since this drug suppresses the central nervous system.</p>	<p>as prescribed.</p> <p>If the patient has taken two prescribed doses of tramadol by mistake, there will be no significant negative effect, but if you have taken a dose significantly higher than the recommended one, signs of intoxication may occur: consciousness disturbances, epileptic seizures, blood pressure fall, rapid heartbeat, narrow or dilated pupils, difficult breathing. In this case contact your doctor immediately or go to the nearest hospital.</p> <p>Like all medicines, this medicine can cause side effects, although not everybody gets them.</p>
Dependence, withdrawal syndrome, tolerance, abuse	<p>Event listed in PIL.</p> <p><u>Drug dependence</u> means that a person needs a drug to function normally. Abruptly stopping the drug leads to withdrawal symptoms. Drug addiction is the compulsive use of a substance, despite its negative or dangerous effects.</p> <p>A person may have a physical dependence on a substance without having an addiction. Some other drugs can cause addiction without leading to physical dependence.</p> <p><u>Withdrawal syndrome</u>, also called a discontinuation syndrome, occurs in drug and alcohol addicted individuals who discontinue or reduce the use of their drug of choice. The risk of a discontinuation syndrome occurring increases with dosage and length of use. The process of eliminating drugs and alcohol from the body is known as</p>	<p>Routine pharmacovigilance is sufficient.</p> <p>By monitoring for early symptoms.</p> <p>The proposed PIL contains the following information:</p> <p>If tramadol is taken over a long period of time dependence may occur, although the risk is very low. When treatment is stopped abruptly, signs of withdrawal may appear.</p> <p>With prolonged use, the effect of tramadol may subside and higher doses must be taken (development of tolerance). In patients with a tendency to drug abuse or drug dependence, treatment with tramadol should only be for short periods and under strict medical supervision.</p> <p>Like all medicines, this medicine can cause side effects, although not everybody gets them.</p>

1.8.2 clean	Tramadol hydrochloride
Risk Management System	capsules, hard

	<p>detoxification. Anxiety, insomnia, nausea, perspiration, body aches, and tremors are just a few of the physical and psychological symptoms of drug and alcohol withdrawal that may occur during detoxification.</p> <p>Long-term use of high doses of tramadol may be associated with <i>physical dependence</i> and a withdrawal syndrome. Some people may experience withdrawal symptoms when they stop taking tramadol. These may include feeling agitated, anxious, nervous or shaky, or having difficulty sleeping.</p> <p>When drugs are used repeatedly over time, <i>tolerance</i> may develop. Tolerance occurs when the person no longer responds to the drug in the way that person initially responded. Stated another way, it takes a higher dose of the drug to achieve the same level of response achieved initially. The development of tolerance is not addiction, although many drugs that produce tolerance also have addictive potential.</p> <p><i>Drug abuse</i> can lead to drug dependence or addiction. People who use drugs for pain relief may become dependent, although this is rare in those who don't have a history of addiction.</p> <p>Treatment with tramadol is not recommended in patients with a tendency to abuse drugs or a history of drug dependence, and in patients who are chronically using opioids.</p>	
Concomitant use with anticoagulants	<p>Event listed in PIL.</p> <p>Tramadol may increase</p>	<p>Routine pharmacovigilance is sufficient.</p> <p>By monitoring for early</p>

1.8.2 clean	Tramadol hydrochloride
Risk Management System	capsules, hard

	<p>anticoagulant effect of anticoagulant therapy.</p> <p>Caution should be exercised during concomitant treatment with tramadol and coumarin derivatives (e.g. warfarin) due to reports of increased INR (The international normalised ratio = INR is a laboratory measurement of how long it takes blood to form a clot. It is used to determine the effects of oral anticoagulants on the clotting system.) and ecchymoses (skin discoloration caused by the escape of blood into the tissues from ruptured blood vessels; ecchymoses can occur in mucous membranes, for example, in the mouth) in some patients.</p>	<p>symptoms.</p> <p>The proposed PIL contains the following information:</p> <p>Taking coumarin anticoagulants (medicines for blood thinning), e.g. warfarin, together with tramadol may affect blood clotting and bleeding may occur.</p> <p>Patients should tell their doctor or pharmacist if they are taking, have recently taken medicines for preventing blood clotting (warfarin).</p> <p>Like all medicines, this medicine can cause side effects, although not everybody gets them.</p>
<p>Serotonin syndrome during concomitant use with serotonergic drugs</p>	<p>Event listed in PIL.</p> <p><u>Serotonin syndrome</u> occurs when the body has too much serotonin, a chemical found in the nervous system. Serotonin syndrome symptoms may include restlessness, hallucinations, loss of coordination, fast heartbeat, rapid changes in blood pressure, increased body temperature, overactive reflexes, nausea, vomiting, and diarrhea.</p> <p>Patients should be informed that tramadol may cause seizures and/or serotonin syndrome with concomitant use of serotonergic agents (including SSRIs, SNRIs, and triptans) or drugs that significantly reduce the metabolic clearance of tramadol.</p> <p>If concomitant treatment of tramadol with a drug affecting the serotonergic neurotransmitter system is clinically warranted, careful observation of the patient is</p>	<p>Routine pharmacovigilance is sufficient.</p> <p>By monitoring for early symptoms.</p> <p>Patients should tell their doctor or pharmacist if they are taking, have recently taken certain antidepressants. Tramadol may interact with these medicines and you may experience symptoms such as involuntary, rhythmic contractions of muscles, including the muscles that control movement of the eye, agitation, excessive sweating, tremor, exaggeration of reflexes, increased muscle tension, body temperature above 38°C.</p> <p>Like all medicines, this medicine can cause side effects, although not everybody gets them.</p>

RMS001320_2	12.12.2016 - Updated: 21.07.2017 - CONFIDENTIAL	Page 48 of 50
-------------	---	---------------

1.8.2 clean	Tramadol hydrochloride
Risk Management System	capsules, hard

	advised, particularly during treatment initiation and dose increases.	
Concomitant use with CNS depressants	<p>Event listed in PIL.</p> <p><i>CNS depressants</i>, sometimes referred to as sedatives and tranquilizers, are substances that can slow brain activity. This property makes them useful for treating anxiety and sleep disorders.</p> <p>Risk of central nervous system and respiratory depression may be increased with the concomitant use of tramadol. Patients have to use tramadol with caution and in reduced dosages. Patients also have to avoid alcohol.</p>	<p>Routine pharmacovigilance is sufficient.</p> <p>By monitoring for early symptoms.</p> <p>The proposed PIL contains the following information:</p> <p>Patients should tell their doctor or pharmacist if they are taking, have recently taken central nervous system depressants (anaesthetics, medicines for treating depressive disorders, medicines for treating mental disorders, sedatives, hypnotics).</p> <p>Like all medicines, this medicine can cause side effects, although not everybody gets them.</p>

Important potential risks

Risk	What is known
Use in patients with a tendency of prolonged elimination (elderly above over 75 years or hepatic/renal impairment)	<p>In elderly patients over 75 years, elimination may be prolonged. Therefore, if necessary, the dosage interval is to be extended according to the patient's requirements.</p> <p>In patients over 75 years of age, daily doses higher than 300 mg are not recommended.</p>
Use during pregnancy and breast-feeding	<p>If patient are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby, they should ask their doctor or pharmacist for advice before taking this medicine.</p> <p>Safety of use during pregnancy has not been studied. High doses or prolonged use during pregnancy may have harmful effects on the foetus or newborn baby.</p> <p>If tramadol is taken during breast-feeding, it should be kept in mind that about 0.1% of the medicine passes into breast milk. A single dose of tramadol usually does not require discontinuation of breast-feeding.</p>

Missing information

Risk	What is known
RMS001320_2	12.12.2016 - Updated: 21.07.2017 - CONFIDENTIAL

Page 49 of 50

1.8.2 clean	Tramadol hydrochloride
Risk Management System	capsules, hard

Use in paediatric population under 14 years of age	Tramadol is not intended for use in children under 14 years of age.
---	---

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.

VI.2.6 Planned post authorisation development plan

Not applicable. No postauthorisation studies are planned.

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

Not applicable, RMP versions 1.0 and 1.1 have not been confirmed yet.

Part VII - Annexes

Annex 1 – EudraVigilance Interface

Not applicable.

Annex 2 - SmPC & Package Leaflet

Please see attached document.

Annex 3 - Worldwide marketing authorisation by country (including EEA)

Please see attached document.

Annex 4 - Synopsis of on-going and completed clinical trial programme

Not applicable.

RMS001320_2	12.12.2016 - Updated: 21.07.2017 - CONFIDENTIAL	Page 50 of 50
-------------	---	---------------