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Summary of the risk management plan (RMP) for Zalviso (sufentanil)

This is a summary of the risk management plan (RMP) for Zalviso, which details the measures to be taken in order to ensure that Zalviso is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Zalviso, which can be found on Zalviso's EPAR page.

Overview of disease epidemiology

Zalviso is an opioid (a strong painkiller) that is used in hospital to treat adults with pain following surgery. Moderately severe acute (short-term) pain occurs in as many as 30% of patients following major surgery with an additional 11% of patients experiencing severe pain. If left untreated, pain following surgery can result in delayed wound healing, extended hospital stay, development of chronic (long-term) pain syndromes and cause other medical problems.

Summary of treatment benefits

Zalviso contains the active substance sufentanil, and is available as tablets to be dissolved under the tongue (sublingual tablets), which are supplied by a special device operated by patients. Its benefits have been shown in three main studies, as well as by supportive data from a reference medicine called Sufenta, which contains the same active substance but is given by injection.

One main study involved 178 patients who had abdominal surgery (surgery on the belly) and another involved 426 patients who had surgery on the knee or hip. In both cases Zalviso was compared with placebo (a dummy treatment). The main measure of effectiveness was based on a patient score that measured the decrease in intensity of pain over 48 hours of treatment. For abdominal surgery, the average decrease in pain intensity was 50 points greater with Zalviso than with placebo (106 versus 56). For knee and hip surgery the decrease in pain intensity was around 88 points greater with Zalviso (76 versus -11) than with placebo.

A third main study compared Zalviso with a patient-controlled pain relief system using morphine, another opioid, and involved 359 patients who had undergone major abdominal, knee or hip surgery. Of 177 patients using Zalviso, 139 rated their pain control as excellent or good (79%), compared with 118 of 180 (66%) using morphine.

Unknowns relating to treatment benefits

In clinical studies most patients were Caucasians with half of patients aged over 65 years. The number of doses and duration of treatment was in line with what is expected for management of acute moderate to severe pain following surgery. There is limited information on safety and effectiveness in patients with reduced kidney or liver function. Zalviso is not recommended in women who are pregnant or breastfeeding, and there is no information on use in such patients.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Slow or shallow breathing (respiratory depression)	Like other opioid medicines, Zalviso can cause slow and/or shallow breathing, which has been reported in up to 1 patient in 10 given sufentanil. The risk is increased if patients take too many doses or use Zalviso at the same time as other medicines that can worsen its effects on breathing (such as certain antidepressants, anxiety medicines and antipsychotic medicines).	The product information contains warnings for patients and healthcare professionals about the possible risk of severe breathing problems with Zalviso. Healthcare professionals should monitor patients' breathing and level of sedation during treatment. Patients should inform their healthcare professional about any other medicines they are taking before using Zalviso.
Allergic reactions	Allergic reactions were not seen in patients during clinical trials with Zalviso. However allergic reactions are known to occur in up to 1 patient in 100 given the active substance sufentanil and in some cases have been severe. In addition, the medicine contains the colouring agent sunset yellow FCF (E110) to which allergic reactions have been reported.	Patients known to be allergic to any of the constituents should not be treated with Zalviso. The product information contains warnings for healthcare professionals and patients about the risk of allergic reactions.

Important potential risks

Risk	What is known
Drug abuse and drug diversion	Like other opioids sufentanil, the active substance in Zalviso, may be subject to abuse (misuse) and diversion (illegal use for recreational purposes). Because Zalviso is given in hospital by a special system that controls the frequency of tablet release, abuse by patients is less likely. However, due to the nature of the medicine some people may try to use Zalviso for illegal purposes. The product information warns about the potential risk of abuse and diversion with Zalviso.
Use for conditions for which the medicine is not licensed, including use in children (off-label use)	There is a risk that healthcare professionals may use Zalviso for conditions which are not licensed including breakthrough pain in cancer patients, long term pain or for use in children. The safety and efficacy of Zalviso has not been investigated for such uses and therefore it is not recommended.
Overdose	Although overdose is a risk with opioids in general, the patient-controlled system for delivering Zalviso has a 20 minute lock-out period between dose administrations to prevent overdose. There may still be a risk of overdose in patients who require lower doses, for example because they have reduced kidney or liver function and do not metabolise (break down) or remove the medicine from the body as quickly as others with normal function. There is an

Risk	What is known
	effective antidote for cases of severe overdose.
Slow heart rate (bradycardia)	Opioids can slow heart rate to less than 60 beats per minute with symptoms of dizziness, weakness, tiredness and sometimes fainting. Patients with a previous episode of slow heart rate or a current condition may have a greater risk of slow heart rate and should take care when using Zalviso.
Low blood pressure (hypotension)	Opioids may cause low blood pressure especially in patients with a low volume of blood plasma (hypovolaemia). Patients who are at risk may receive treatment to maintain their blood pressure at a stable level when using Zalviso.
Paralysis of the gut (paralytic ileus)	Opioids can slow and even stop movement within the gastrointestinal tract (gut), which affects its normal function and may cause pain. Patients who have a higher risk of paralysis of the gut include those who already have a bowel disorder or who have recently undergone major stomach surgery. Doctors should use Zalviso with care in such cases.
Spasm of the sphincter muscle (spasm of sphincter of Oddi)	Opioids can cause spasm of the sphincter muscle which normally controls the flow of pancreatic juices and bile into the small intestine. This causes a blockage of the pancreatic juices and bile leading to stomach pain. Patients with biliary tract disease and acute pancreatitis may have a greater risk and doctors should use Zalviso with care in such cases.
Convulsions	Opioids can cause convulsions through their effects on the brain, and with some opioids this is more likely with longer term use. Zalviso is not intended for long term use but it is possible that sufentanil may cause convulsions.
Use in patients with increased pressure in the brain (raised intracranial pressure)	Opioids may cause small short term increases in pressure in the brain. Patients with reduced consciousness, head injuries or brain tumours are at greater risk and doctors should use Zalviso with care in such cases.
Device failure to dispense tablets correctly	There is a possibility that the special device for delivering Zalviso may not function as expected. If the device stops delivering tablets, a temporary period where the pain is not relieved may occur. Potentially, the device might deliver more than one tablet at once, or deliver the next tablet in less than 20 minutes, exposing the patient to symptoms of overdose or other adverse reactions.

Missing information

Risk	What is known
Limited information on use during pregnancy	There are no data on the use of Zalviso in pregnant women and data on use of sufentanil by injection are limited apart from during labour. Sufentanil can cross the placenta and therefore Zalviso is not recommended during pregnancy or in women of childbearing potential not using contraception.
Limited information on use during breastfeeding	Sufentanil is known to pass into human milk when given by injection and therefore the prescriber should apply caution when treating a woman with Zalviso who is breastfeeding. Breastfeeding is not advised with use of sufentanil because of the possible risk of adverse effects in breastfed

Risk	What is known
	newborns or infants.
Limited information on use in patients with liver and/or kidney problems	In clinical trials around 1 patient in 20 had mild to moderate liver or kidney problems. No patients had severe liver or kidney problems and information on safety and effectiveness in such patients is lacking. Patients with liver or kidney problems using Zalviso should be monitored for symptoms of overdose.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for X can be found on Zalviso's EPAR page.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material can be found in Annex II of the product information which is published on Zalviso's EPAR page; how they are implemented in each country however will depend upon agreement between the marketing authorisation holder and the national authorities.

These additional risk minimisation measures are for the following risks:

Use for conditions for which the medicine is not licensed, overdose and device failure

Risk minimisation measure: Educational materials for healthcare professionals
Objective and rationale: To increase healthcare professionals understanding of the intended use of Zalviso, and how to minimise the risk of overdose
Description: Educational materials will provide instructions on the intended use of the medicine and the available guidance in the product information, plus how to choose suitable patients and the potential risks associated with the improper functioning of the device, thereby helping reduce the risks and assist safe and appropriate treatment.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	**Objectives**	**Safety concerns / efficacy issue addressed**	**Status**	**Planned date for submission of (interim and) final results**
The usefulness of the educational materials for HCPs to ensure appropriate use of Zalviso and minimize the risks will be evaluated in a survey.	1. To evaluate whether the educational materials have been provided to HCP through tracking distribution and documenting where HCPs training has been performed prior to use of Zalviso as an indicator of product comprehension including awareness of off-label use (including paediatric use), device failure and overdose. 2. To assess whether HCP followed the guidance provided in the educational materials through a survey in selected medical centres across EU countries 6 months to 2 years after launch (depending on market penetration and use of Zalviso) to capture the understanding of appropriate use of the product.	Off-label use (including paediatric use), device failure and overdose	Planned	Outcome to be presented in PSURs according to PSUR submission timelines

Studies which are a condition of the marketing authorisation

There are no studies which are a condition of the marketing authorisation.

Summary of changes to the risk management plan over time

Major changes to the Risk Management Plan over time

Not applicable.

This summary was last updated in 08-2015.