IN USE PRODUCT SAFETY ASSESSMENT REPORT FOR ZALVISO® (SUFENTANIL CITRATE) 15 MICROGRAMS SUBLINGUAL TABLETS

SUMMARY OF ASSESSMENT AND ITS FINDINGS

BACKGROUND

Zalviso® sublingual tablets are licensed for the management of acute moderate to severe post-operative pain in adults in a hospital setting only (1). Zalviso® (sufentanil 15 micrograms) sublingual tablets are dispensed via a self-managed tablet delivery system which is pre-programmed to dispense a single sublingual tablet on a patient-controlled, as needed basis. The Zalviso® delivery system is the first sublingual analgesia delivery system available in the UK to be used on a patient controlled basis; it was launched in September 2016 (2). Traditional delivery systems for patient controlled analgesia (PCA) are intravenous. This new controlled delivery system will be unfamiliar to NHS healthcare professionals. The potential medicine safety issues of this novel delivery system of a class 2 controlled drug are considered in this product safety review.

DETAILS OF PRODUCT (S) ASSESSED

The product assessed using the validated UKMi product assessment tool was (3): Zalviso® (sufentanil 15 micrograms) sublingual tablet delivery system; Grünenthal Limited.

The Zalviso® delivery system includes:

- Zalviso® controller device
- Dispenser and cap (disposable mouthpiece)
- Holster for the Zalviso® controller device
- Drug cartridge
- Security tether
- Authorised access card
- Radio Frequency Identification (RFID) thumb tag (disposable) (4)

A formal assessment of the device and associated items were not undertaken.

Assessments were carried out with reference to: product demonstration by Grünenthal Limited; product images; summary of product characteristics (SmPC) and packaging inserts; instructions for use and additional risk minimisation material supplied by Grünenthal Limited (1,4-7).

CONCLUSION FOLLOWING APPLICATION OF VALIDATED ASSESSMENT TOOL

Zalviso® is for use in a hospital setting for pain related to post-surgical procedures only (in adults). It should only be prescribed by physicians who are experienced in the management of opioid therapy. The administration device delivers a single sufentanil 15 micrograms sublingual tablet with a 20 minute lockout interval between doses, over a maximum recommended duration of up to 72 hours (1). A single sufentanil 15 micrograms sublingual tablet is considered equivalent to 3 milligrams intravenous morphine (8).

The following medicines safety considerations were raised from the risk assessment; mitigating and other necessary actions are considered in the next section.

Controlled drug status

- Sufentanil is a schedule 2 controlled drug (CD) and hence has specific legal requirements associated with it, including storage requirements, record keeping in a controlled drug register and prescription requirements (9).
- There should be restricted access to the 'authorised access card' which allows healthcare professionals to operate and set the device up for patient use. The access card includes a slot to enable hanging on keys for the CD cupboard.
- When treatment is discontinued any sufentanil tablets remaining in cartridges should be removed and

destroyed as per local CD medicines policies.

Look and sound-alike names

There is potential for sound and look alike name confusion between sufentanil and fentanyl. Fentanyl is available as sublingual tablets of strengths: 100mcg, 200mcg, 300mcg, 400mcg, 600mcg, 800mcg and buccal: 100mcg, 200mcg, 400mcg, 600mcg and 800mcg (9). In practice, confusion with fentanyl resulting in medication errors is unlikely as sufentanil sublingual tablets are available in a different strength (15 micrograms), packaged in cartridges and the route of administration is via the Zalviso® delivery system only.

Safety features

Zalviso® (sufentanil 15 micrograms) sublingual tablets are dispensed via a self-managed tablet delivery system which consists of several safety features which include:

- A reusable device designed to operate only with cartridges containing sufentanil tablets, which can be used for up to 750 cartridges. The device delivers a single sufentanil 15mcg tablet with a minimum of 20 minutes lockout interval between doses i.e. a maximum of 3 doses in one hour. The device is set to a maximum 72 hours of use or up to 3 cartridges (120 tablets; 40 in each cartridge), whichever comes first. In the event of repeated maximal usage, three cartridges will last for a period of 40 hours (1,2,6). Doses cannot be adjusted or the device programmed to extend the minimum interval between doses
  There is the possibility that the device might not function as expected with potential to deliver more than one tablet at once, before the 20 minute lockout period or not deliver a dose at all (10). Currently, there is no experience of the device in the delivery of other products.
- A device electronic storage system which collates data on quantity of doses delivered, doses delivered per staff shift, number of doses remaining and any attempted doses during the lockout period. The device cannot be overridden to increase frequency of dispensing (6,11).
- Authorised access card restricted to healthcare professionals to operate and set the device up for patient use. The card does not allow the healthcare professional to dispense a tablet (6,11).
- Visible and audible alarms indicating if the dispenser has been pried from the controller (6).
- An adhesive thumb tag with radiofrequency identification that pairs the patient to the device to operate and dispense the tablets, reducing the risk of 'proxy' dosing. However, there is a concern of patients removing the thumb tag, diversion of tablets dispensed, as well as tablet misplacement. The thumb tag should not be exposed to strong magnetic fields and therefore should be removed before an MRI and other such procedures (6).
- A security tether for device attachment to the patient's bedrail or other secure object nearby. This will prevent the device being removed from the ward. Once the device is attached to the security tether, sufentanil tablets can be dispensed (6).

Training

Specific training is required to operate the Zalviso® delivery system and only those healthcare professionals who have received the training should conduct patient demonstration and instruction on use. It is anticipated the training burden to be no more than what is required to train healthcare staff on the use of intravenous PCA.

Method of administration

- Zalviso® tablets are for sublingual use only. They are self-administered using the administration device with the disposable mouthpiece. The tablet dissolves under the tongue and should not be crushed, chewed or swallowed. Patients should not eat or drink and minimise talking for 10 minute after each dose (1, 2).
- There is a risk of tablet misplacement once the tablets have been dispensed, or for patients to inadvertently swallow the tablet or place buccally. This could result in a lack of effect or an increase in adverse effects due to the difference in bioavailability for the various routes of administration: buccal (78%), sublingual (59%), oral (9%) (1,2).
- Patients must be assessed for their ability to operate the Zalviso® delivery system appropriately. The patient should have the ability to hold the device upright and individual patient factors such as visual/cognitive issues considered, as well as history of alcohol or opioid abuse. The SPC advises the potential for abuse should be considered (1,6).

Product packaging and literature

A suite of manufacturer product literature exists to support the correct use and administration of Zalviso®(1,4-7,12):

- Summary of Product Characteristics
- A 'set up guide'
- Instructions for use
- Risk minimisation material (a basic administration guide)
- A patient information leaflet and reference sheet

Pharmacovigilance and adverse events

- Zalviso® is not a black triangle and therefore is not under intensive regulatory surveillance. The European Public Assessment Report states the risk associated with the sufentanil medicinal product are consistent with other opioids, including the adverse event profile and the abuse potential (13).
- Sufentanil is a potent opioid, 500 to 1000 fold higher than oral morphine, and with highly selective binding to μ–opioid receptors. Naloxone is used as an antidote to reverse the respiratory depression caused by sufentanil in the event of deliberate or inadvertent overdose. However, the long half-life of sufentanil: 6-10 hours after a single dose and 18 hours after repeated dosing, should be taken into account in relation to the shorter duration of activity with naloxone (1)
- The delivery system includes an adhesive thumb tag containing tan polyurethane nonwoven adhesive (2). Patients should therefore be asked their allergy status to plasters before use.

Shelf-life and stability

The sufentanil containing cartridges are packed in sachets containing oxygen absorber (5). Once removed from the sachet the cartridge should be used within 72 hours as per product licence (2).

In summary, the Zalviso® self-managed tablet delivery system provides the option of a non-invasive alternative to intravenous PCA. Potential advantages include improved mobility for patients and avoidance of delays in treatments associated with cannulation for intravenous therapy. However these advantages should be considered in the context of increased training burden with the introduction of a new device and the limited data on some patient groups (for example, those on chronic opioid therapy and/or history of alcohol or opioid abuse were excluded in the phase 3 trials, and only limited data exists for use in severe renal and hepatic impairment) (1,11). In addition, self-administration of sublingual therapy using a tablet delivery system can introduce other safety risks such as unfamiliarity and in-use experience with the delivery system, device failure, mis-dosing and risk of tablet diversion. Currently there is limited use of Zalviso® tablet delivery system in the NHS to confirm the safety and reliability of it in practice; data is derived from trials conducted in the US.

POTENTIAL NEXT STEPS AND MITIGATION ACTIONS

There is significant implementation work that will be need to be carried out locally to support safe use of Zalviso® (sufentanil) self-managed tablet delivery system. NHS Healthcare providers should consider a number of actions:

Prepare a business case to submit to local Drugs and Therapeutics committees. The Manufacturer's Zalviso® resource centre is a useful source of information; http://www.zalviso.co.uk/resource-centre/. Specialist pain management teams are integral in the preparation of the business case. The business case may include:

- Defining suitable patient groups and criteria
- Defining which health care professionals are trained to use the system
- The number of devices likely to be used in the organisation
- A local medication safety risk assessment
- Cost impact [the NHS list price per cartridge (40 tablets): £53.25; contracts for the supply of the Zalviso® system are negotiated with individual Trusts] (2)

Develop local protocols for the use of Zalviso® self-managed tablet delivery system. This may include (but not exhaustive):

- Training programmes to include (but not limited to) a designated trainer, a 'checklist and sign-off' for trained nurses, a register of trained nurses that can operate the device
- A patient assessment criteria for their ability to operate the device
- A list of designated areas for storage of the device
- Systems for the security of the product when in-use as well as security of the authorised access card
- Systems for storage, ordering, supplying and disposal of the drug cartridges
- Appropriate paperwork for recording observations and care plans

- Reference to related policies such as controlled drug policies and management of opioid toxicity
- A procedure for out of hours support

Pilot the use of the Zalviso® delivery systems in a designated area or speciality to establish safe working practices before rolling out to further surgical areas.

Report suspected adverse drug reactions and medication errors to the Medicines and Healthcare Products Regulatory Agency (MHRA) via the Yellow Card Scheme/ National Reporting and Learning System (NRLS) via local reporting mechanisms such as Datix.

Conduct research audits to assess the in-use safety of the Zalviso® self-managed tablet delivery system for post-operative pain in UK clinical practice.

This report was produced in April 2018.

This report summarises product assessments undertaken by:
London Medicines Information Service and Welsh Medicines Information Service. For comments email lnwh-tr.medinfo@nhs.net

We are also grateful for the input of clinical specialists (pain team, surgery) and UKCPA Pain Management Group in completing this piece of work.

The UKMI product safety assessment group would appreciate your views on the usefulness of this report. We have devised a short survey which we would appreciate you completing, it should take approximately 10 minutes to complete. Click the following link to complete the survey:
https://www.surveymonkey.com/r/UKMiProductSafetyAssessments.

References

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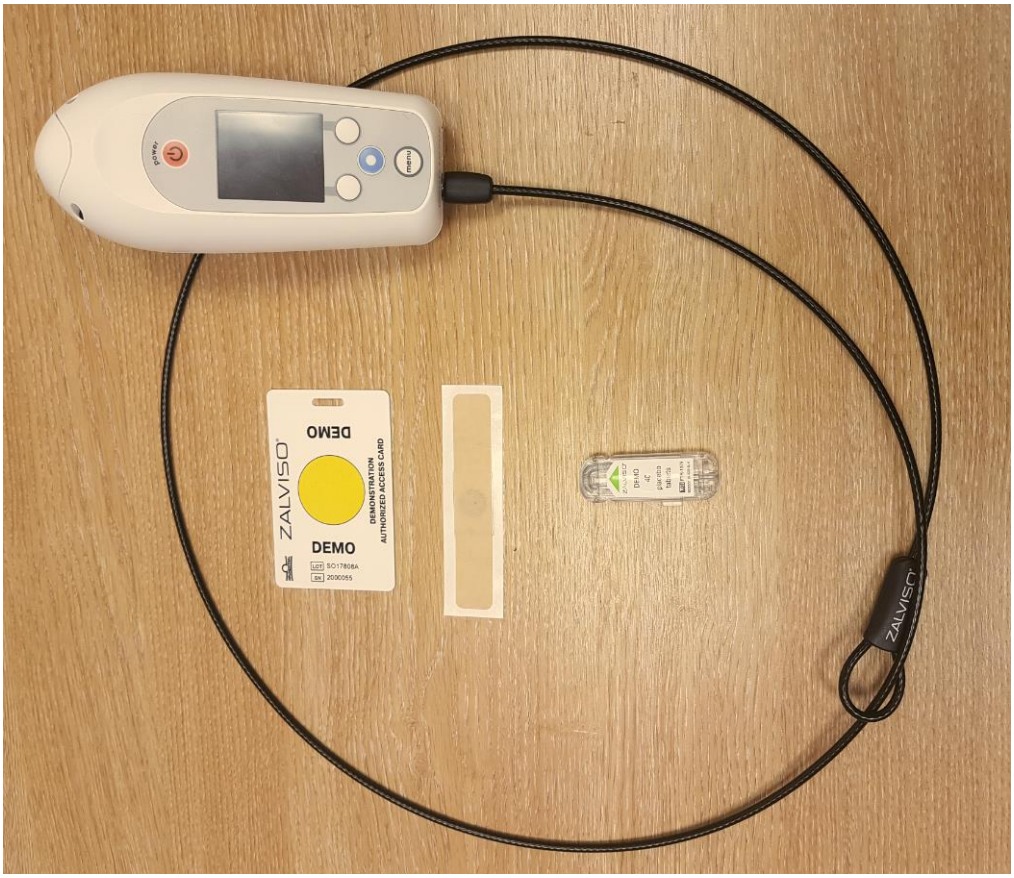
APPENDIX 1: PRODUCT IMAGES

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