European Medicines Agency

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ASSESSMENT REPORT
FOR
IONSYS

International Nonproprietary Name:
FENTANYL HYDROCHLORIDE

Procedure No. EMEA/H/612/A20/0013

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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1. BACKGROUND INFORMATION ON THE PROCEDURE

The European Medicines Agency (EMEA) was made aware on 27 September 2008 by the Marketing Authorisation Holder (MAH), Janssen-Cilag International NV, of the occurrence of a quality defect affecting a single batch of IONSYS.

1.1 Information about the product, use and manufacture

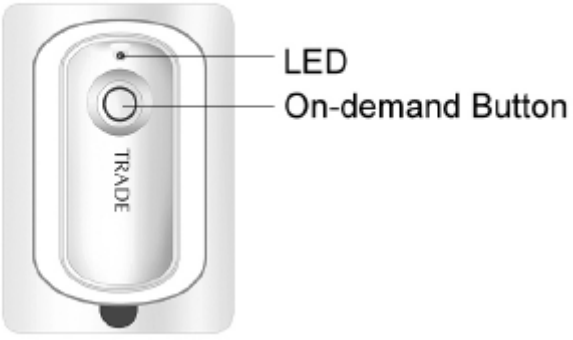
Ionsys is indicated for the management of acute moderate to severe post-operative pain for use in a hospital setting only. It is an iontophoretic transdermal system, which can be activated by the patient in response to pain. Each system contains 10.8 mg fentanyl hydrochloride equivalent to 9.7 mg of fentanyl and delivers 40 micrograms fentanyl per dose, to a maximum of 3.2 mg (80 doses). The product delivers 40 µg per on-demand dose up to a maximum of 240 µg (6 doses each of 10 minutes duration) per hour but not more than a maximum of 80 doses within a 24 hour period.

Fentanyl is a synthetic opioid related to the phenylpiperidine class of compounds. It is a highly sensitive µ-receptor agonist and is about 100 times more potent than morphine as an analgesic. Opioids exert their therapeutic effects by mimicking the action of endogenous opioid peptides at opioid receptors. Effects on both local neurons and intrinsic pain modulating circuitry lead to analgesia and other therapeutic effects as well as undesirable side effects, the most serious of which is respiratory depression.

Ionsys consists of a top housing assembly (device component) and a bottom housing assembly (drug component). The top housing assembly is composed of an injection-molded plastic component that protects the electronics and a printed circuit board assembly (PCBA). Audible tones and a LED are used to indicate dose delivery, duration, number of doses and also to alert the patient to problems with the system.

The bottom housing assembly consists of a thermoformed unit containing electrodes and active substance in gels which include a solvent, a matrix polymer, buffering agents and an antimicrobial agentA release liner (siliconized polyester film) covers the skin adhesive and both hydrogel formulations and is removed before use. Each iontophoretic transdermal system is packed in a heat sealed sachet that contains a moisture absorber.

Figure 1: Topside view of IONSYS system



Ionsys is manufactured in the U.S.A. The product also undergoes full QC testing at the finished product manufacturer prior to shipment to Europe.

The product is manufactured in five major steps: (1) hydrogel mixing; (2) preparation of the bottom assembly; (3) curing; (4) final assembly; (5) packaging. Each system is inspected and tested to verify functionality prior to placement inside a heat sealed pouch along with a moisture absorber packet for primary packaging.

1.2 Regulatory history of the product

The product was first authorised following CHMP positive opinion on 24 January 2006. During the initial assessment, non-functioning devices were observed during stability studies and corrosion of switches was identified as a possible cause. The MAH made design changes in order to improve reliability. Stability data indicated that at storage conditions below 25 °C no non-functioning systems were found and a 6 month shelf-life was accepted. Furthermore, afunctionality test was included in the finished product specifications and an instruction was given to the dispensing pharmacist to perform a functionality test prior to dispensing.

During the initial assessment the possibility of self-initiating systems was not reported or discussed. Corrosion within the device was considered to cause battery depletion resulting in a non-functioning system. Other device malfunctions such as low output voltage or high output current, which might affect drug delivery, would result in a type II error (four beeps repeating continuously) and the system would shut down as a safety precaution. Therefore, it was considered that any device defects would result in the product failing 'safely'.

On 9 July 2007 a meeting was held between the Rapporteur and the MAH. During this meeting the MAH indicated that IONSYS had not been commercialised, because continuing problems were occurring with a manufacturing issue leading to corrosion, specifically of the switch on the printed circuit board. The result of this corrosion was a system malfunction that resulted in non-initiating systems (NIS) and, occasionally, self-initiating systems (SIS). It was explained that water from the hydrogels evaporated into the sealed pouch head space leading to moisture condensing on the printed circuit board and corrosion of the switch. In some circumstances, it had been observed that this induced an intermittent voltage consistent with dose activation and resulting in SIS. A solution to the problem, the inclusion of a moisture absorber, was proposed by the MAH. The Rapporteur agreed, in principle, and requested the MAH to provide written confirmation to the CHMP that the product would not be launched until sufficient data were available to support the approval of a type II variation to address the issue.

On 19 August 2007 a Type II variation was submitted to change the immediate packaging of the finished product to include a moisture absorber. Stability data were provided for three commercial scale batches stored at long term (25 ± 2°C / 60 ± 5% RH), intermediate (30 ± 2°C / 65 ± 5% RH) and accelerated (40 ± 2°C / 15 ± 5% RH) conditions for 6 months (equal to the shelf-life of the product). Product quality attributes were within specifications and no self-initiating systems were observed during testing.

On 2 June 2008 a Type IB variation was approved to increase the shelf-life of the product from 6 months to 12 months based on 12 month stability data from the commercial scale batches. Again, no self-initiating systems were reported. Non-initiating systems noted (2 at 30°C/65% RH & 40°C/15%RH respectively) were caused by non-corrosion related single component failure.

1.3 History of the quality defect incident

<u>September 4th 2008:</u>

A report was received from the clinical packager that systems from a batch of IONSYS were beeping which could be considered as an indication of self-initiating systems. The systems had been sent to the clinical packager to be over labelled for clinical purposes. In order for an IONSYS system to be activated, the On-Demand Button must be pressed twice within 3 seconds, after which, an audible beep will occur. As the over labelling process requires that a label is manually applied on the primary packaging (foil pouch) and then firmly adhered via a back and forth motion, it was theorised the report of beeping sounds was due to inadvertent button pushes. The initial investigation identified no testing

or manufacturing issue associated with this lot. However, this theory of inadvertent manual activation during the over labelling process could not be confirmed. To rule out the possibility of Printed Circuit Board (PCB) corrosion a Failure Analysis protocol was initiated on 1170 returned systems from the impacted batch .

September 23 (PM):
A visual observation of signs of corrosion was made in a small number of units of the impacted batch, which had been returned from the clinical packaging site for execution of the above stated protocol. An investigation into the root cause of this occurrence was immediately initiated to determine the scope and any product impact.

September 24 (AM):
A precautionary hold was placed on all commercial distribution. The initial investigation focused on an immediate assessment of customer complaint data and batch processing data. Analytical testing was initiated to determine if the observation was consistent with corrosion that might be a potential precursor to self-activation of the system. The initial investigation also focused on the pedigree of the impacted batch and linkage to quantities distributed commercially.

September 25 (PM):
Analytical test results confirmed the presence of a form of corrosion in some manufacturing site commercial retains for the impacted batch that is a potential precursor to self-activation of the system (SIS).

September 26:
Management notification and execution of recall action committees.

September 27:
A recommendation to initiate a class I recall was made. The class I recall was initiated for all lots of IONSYS distributed commercially and within expiry on September 28 2008. At this point the root cause of the defect had not been identified.

The MAH was therefore asked to provide, by 10 November, a complete updated investigation report addressing the below points, for assessment and consideration of any necessary regulatory actions by the CHMP for its November 2008 meeting:

- Background detailed information (e.g. information about the product, its manufacturing process and/or use and the complete supply chain for the affected parts of the product)
- History of the incident with specific dates when it occurred and/or was observed
- Figures and trends of the numbers of affected units
- Potential root cause, discussing the possible connections with the previous corrosion problems discussed during assessment of the original application and subsequent variations
- Corrective and preventive actions taken or to be taken to eliminate the root cause.
- Review of complaint records for reports of similar defects.
- Review of all associated batch manufacturing, packaging, testing (investigation testing or regular stability testing), release and distribution records for anomalies which may explain the suspected defect
- Examination, and retesting, if appropriate, of retained samples.
- Explain whether and if so why the problem is restricted only to those products/lots identified.
- Overall conclusions

The outcome of the updated MAH investigation report received on the 10th November 2008 was that the root cause analysis of the product defect was still on-going with a large number of recalled units not yet returned to the manufacturing site for investigation. No unusual issues with the manufacturing and testing of the finished product or its components had been identified except for corrosion of the PCBA.

Given the re-occurrence of technical difficulties with the device and taking into consideration the potential safety risks associated with the self-initiation of the system, the most serious effect being respiratory depression, which could lead to death, a thorough review was required to ensure sufficient evidence is available and to ensure a consistent high level of quality and safety of the medicinal product.

In view of the above the European Commission initiated a procedure under Article 20 of Regulation (EC) No 726/2004. The European Commission requested the Committee on 19 November 2009 to assess the above concerns and its impact on the risk/benefit balance for Ionsys, and to give its opinion on measures necessary to ensure the safe and effective use of and on whether the marketing authorisation for this product should be maintained, varied, suspended or withdrawn.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

The MAH has initiated a root cause analysis to identify and confirm possible factors that could contribute to corrosion on the printed circuit board assembly (PCBA) of the product. Based upon current reviews of quality data, product evaluations, and previously investigated failure modes, the MAH has focussed on three primary areas.

1) Final IONSYS system assembly
2) Printed Circuit Board Assembly (PCBA) manufacture
3) Moisture absorber manufacture

The investigation will be inclusive of all lots since product introduction

Quality Data Review

Since the marketing of the product in January 2008, functional complaint field reports have been received at a rate that is within anticipated report levels and there are no trends with complaint category or lot number.

There have been 10 functional complaint field reports for which defects have been confirmed. Only one of these reports concerned corrosion to the PCBA board, with the potential for self-initiation (which was from the impacted batch that prompted the recall).

After the recall, a complaint report was received regarding a unit fromanother batch, which had a flashing LED without being activated i.e. potential self-initiation of the unit. The PCBA board was found to have full functionality and no corrosion or other discrepancy was found.

Manufacturing, QC testing and EU release testing

Review of all associated batch manufacturing, packaging, testing, release testing and distribution records has not identified an issue or discrepancy that may explain this occurrence. All batches have been manufactured, tested, and released in accordance with all requirements and specifications. This includes 100% functional screening of each unit and 100% weight verification to ensure each pouch contains a moisture absorber packet.

Stability review

The first three commercially produced lots were placed on stability for evaluation and have not shown any issues to date (9 months). A review of the analytical records revealed nothing unusual that could have caused the corrosion defect.

The MAH has submitted 12 months of stability data for the product in its current marketed form in support of the type 1B variation to extend the shelf life from 6 months to 12 months. No significant trends were observed over time, except for a decrease in adhesion, which was within specification. Electrical and electronic function test data show that the product device performs consistently over time. At 30°C/65% RH, one non-initiating system (NIS) out of 315 units tested was detected at 3 months and 12 months (different batches); at 40°C/15%RH, one non-initiating system (NIS) out of 315 units tested failed at 2 months and 6 months (different batches). No corrosion was observed, and these NIS were attributed to a non-corrosion related single component failure.

Printed Circuit Board Assembly (PCBA)

The MAH has reviewed all batch documentation relating to the PCBA and no potential cause of the defect has been identified; however, the investigation is on going.

The MAH has carried out a visual inspection of the PCBA on reserve samples from 5 lots including the batch that initiated the recall), in addition to the units returned from the clinical packager .

The visual inspection was to determine if corrosion of the PCBA was present.

Summary of Visual Inspection

Of the units from 5 lots inspected one lot had
5 PCBA units (out of 238 units tested) with corrosion defect unlikely to cause self initiation
The lot that initiated the recall had
152 PCBA units (out of 3,090 units tested) with corrosion defect likely to cause self initiation and 406 PCBA units (out of 3,090 units tested) with corrosion defect unlikely to cause self initiation and a final lot had

1 PCBA units (out of 158 units tested) with corrosion defect unlikely to cause self initiation

Corrosion likely to cause self-initiation is when the observed corrosion extends over half way between points of contact and a bridging event is possible. Corrosion unlikely to cause self-initiation is when observed corrosion is less than half way between points of contact and a bridging event is not possible.

SEM analysis has confirmed corrosion likely to cause self-initiation. Additional testing is ongoing. The corrosion observed in the impacted batch was observed on PCBA itself whereas than previously observed corrosion was observed in a different location around the switch.

Moisture Absorber

The moisture absorbers used in the impacted batch complied with quality specification. No issues were observed during the manufacture of the moisture absorber and all units inspected to date have been packed with a moisture absorber (the presence of a moisture absorber is a quality control check that is carried out before the unit is used by a patient, as stated in the SPC)

There are no signs of general moisture condensation in any other parts of the PCBA, indicating a failure in the moisture absorber. The MAH has consequently excluded the moisture absorber as a potential root cause for the defect.

Discussion and Conclusions

The MAH has initiated a root cause analysis of the product defect, which is still ongoing. The MAH has not found any unusual issues with the manufacturing and testing of the finished product or its components except for corrosion of the PCBA. Corrosion of the PCBA is a known precursor to self-initiation of the units. Corrosion of the PCBA likely to cause self-initiation is predominantly observed in theimpacted batch, which prompted the product recall. Corrosion unlikely to cause self-initiation has been observed in other lots..

The MAH has also received another report of a potential self-initiating system, not linked to corrosion of the PCBA, which is a concern given the history of product defects with the PCBA in this product.

Stability data received to date show compliance with the shelf life specification and supports the current shelf life and storage conditions. The PCBA performed consistently over time; only one non-initiating system (NIS) out of 315 units tested were observed four times in the 12 months of real time stability testing provided.

This is the second time where corrosion of the PCBA has been observed, a known precursor to potential self-initiation of the unit, which, given the active substance, may increase the likelihood of overdose and/or respiratory depression, leading to death.

The company has acknowledged that they are unable to confirm the specific root cause of the problem at this time. Furthermore, the current quality control strategies in place at both product manufacture and EU QC test sites has been unable to detect PCBAs that have developed corrosion and potential self-initiation of the unit.

2.2 Clinical aspects

Device defects and associated adverse events reported to the competent authorities in the European Union since EU launch date 14th January 2008.

Sources of Data

The CHMP reviewed all the available safety data, including the latest PSUR and a review of the MAH post-marketing database. A search was also performed in the Medicines and Healthcare products Regulatory Agency (MHRA) safety database.

PSUR number 5 (reporting period 01/11/07-30/04/08)

The MAH provided all reports classified under the Injury and poisoning System Organ Class (SOC) and included the term procedural complaints which is not listed in this MedDRA SOC. There were 9 reports of device malfunction; 3 of which were not associated with any adverse event, 4 were associated with application site reactions and 2 reported 'drug ineffective.'

There were no serious adverse events associated with device malfunction, in particular there were no reports of self-activation or overdose as a result.

There were no cases of overdose and/or respiratory depression reported in the PSUR time period..

There was one case described in the line listings as 'hypoventilation' from a 'study' in a 55 year old female but no further details were provided.

Spontaneous reports in the MHRA ADR database

A search performed using the product name 'IONSYS' and the Injury and Poisoning SOC provides no reports for the entire time period of the database.

A search using the generic name, fentanyl, provided 15 reports in the Injury and Poisoning SOC between 31st December 2007 and 29th October 2008. None of the reports were associated with the Ionsys device.

A Business Objects search was performed by the scientific assessor responsible for forwarding device defect reports was conducted. No cases were retrieved.

No cases of overdose and/or respiratory depression associated with the use of Ionsys were retrieved.

Adverse events reported in the MAH's report dated 10/11/2008

A Health Hazard Evaluation report, completed on 29/09/2008 and based on a review of the post marketing safety database for adverse events up to 26/09/2008, found 13 cases reporting overdose and/or respiratory depression associated with fentanyl hydrochloride. None of these cases were serious events or were attributed to a product quality defect. However the cases were not sufficiently documented.to be conclusive.Furthermore, the MAH has reviewed the database up to 28/10/2008 and there were no new cases and no further follow up information on the existing cases.

Conclusion

No serious adverse events associated with the use of Ionsys were reported in the period from 31st December 2007- 29th October 2008. However more details are needed about the 13 cases reporting overdose and/or respiratory depression whilst using Ionsys in an expedited manner.

Adverse events reported in the last MAH PSUR associated with device malfunction were related to lack of efficacy and application site reactions.

There are no cases of device malfunction resulting in self activation of the device and unintentional overdose.

2.3 Action plan

Reconciliation of Product Recall

Reconciliation is complete - 100% of all systems available for return to the MAH from the four lots recalled have been returned.

Communication plan

A Direct Healthcare Professionals Communication designed to inform prescribers and pharmacists of the observed quality defect of the product and the subsequent product recall was sent on 28 September 2008.

3. FOLLOW-UP MEASURES

As a result of the total recall of the product from the market and the CHMP recommendation to suspend the Marketing Authorisation, the MAH informed the Committee of their inability to meet the deadlines agreed for ongoing Follow-up measures (FUMs) until a forward plan for re-introduction onto the market is agreed.

4 OVERALL DISCUSSION AND BENEFIT RISK ASSESSMENT

The MAH has initiated a root cause analysis of the product defect, which is still ongoing. The MAH has not found any unusual issues with the manufacturing and testing of the finished product or its components except for corrosion of the PCBA. Corrosion of the PCBA is a known precursor to self-initiation of the units. Corrosion of the PCBA likely to cause self-initiation is predominantly observed in the impacted batch, which prompted the product recall, although corrosion unlikely to cause self-initiation has been observed in other lots. However, the criteria for defining the likelihood of self-initiation due to corrosion seem to be rather arbitrary.

Adverse events reported in the last PSUR associated with device malfunction were related to lack of efficacy and application site reactions. There are no cases of device malfunction resulting in self activation of the device and unintentional overdose. No serious adverse events associated with the use of Ionsys were reported to the MHRA in the period from 31st December 2007- 29th October 2008.

However, this is the second time in the product lifecycle, where corrosion of the PCBA has been observed, a known precursor to potential self-initiation of the unit, which may increase the likelihood of overdose. The safety concerns associated with a potential overdose are serious, since it may cause respiratory depression, which could lead to death.

In addition the MAH is unable to confirm the specific root cause of the problem at this time. Stability testing of the units has not revealed any further insight into the cause of the defect. Furthermore, the quality control strategies currently in place at both manufacturing and testing sites has been inadequate to detect PCBAs that have developed corrosion and potential self-initiation of the unit and the quality system of the MAH has been unable to resolve the recurrent problems with the PCBA and to prevent the occurrence of this quality defect.

In view of the above data the CHMP considered that at the time of the Opinion, the benefit/ risk balance for Ionsys was negative and recommended the suspension of the Marketing Authorisation until such a time that the MAH can robustly demonstrate the quality of the product.

The MAH has accepted the CHMP recommendation and has not requested an Oral Explanation.

5 CONCLUSION AND GROUNDS FOR THE OPINION

The CHMP reviewed the information provided by the MAH from its investigations into the root cause of the defect. This included background detailed information, history of the incident, potential root cause discussing the possible connections with the previous corrosion problems observed during assessment of the original application and subsequent variations, review of complaint records for reports of similar defects, batch release, QC record and stability data reviews.

The root cause analysis initiated by the MAH is still ongoing and has yet to confirm the specific cause of the defect. No unusual issues with the manufacturing and testing of the finished product or its components have been identified except for corrosion of the printed circuit board assembly (PCBA). Corrosion of the PCBA is a known precursor to potential self-initiation of the unit, which, given the active substance, may increase the likelihood of potential overdose and/or respiratory depression, leading to death.

Given the fact that:

- The root cause of the quality defect has yet to be confirmed
- The existing quality control strategies at both product manufacturing and testing sites for the product was not able to detect PCBAs that have developed corrosion leading potential self-initiation of the unit
- The quality system of the MAH, at that time, has been unable to resolve the problems with the PCBA and to prevent the occurrence of this quality defect.
- The serious side effects that may be caused from the self-initiation of the unit,

the Committee concluded that the benefits of Ionsys do not longer outweigh its risks and therefore recommended the suspension of the Marketing Authorisation.

For the suspension to be lifted, the MAH should provide the Committee with evidence that the quality of the product can be robustly demonstrated.

<u>The following requirements must be fulfilled before the suspension of the MA can be lifted:</u>

- The root cause of the quality defect needs to be confirmed and adequately mitigated.
- It should be demonstrated that the quality control strategies are appropriate to identify detect PCBAs that have developed corrosion leading to malfunctioning or self-initiating units
- It should be demonstrated that the quality system of the MAH is sufficient to prevent the reoccurrence of such a defect
- Details of the 13 cases reporting overdose and/or respiratory depression associated with fentanyl hydrochloride present in the company safety database in an expedited manner should be provided.