

Annex I

**Scientific conclusions and grounds for suspension of the marketing
authorisation**

Overall summary of the scientific evaluation of Kexxtone 32.4 g continuous-release intraruminal device for cattle

1. Introduction

Kexxtone 32.4 g continuous-release intraruminal device for cattle (hereafter named 'Kexxtone') is a veterinary medicinal product (VMP) containing the active substance monensin. It was authorised in 2013 via the centralised procedure and is intended for the reduction in the incidence of ketosis in the peri-parturient dairy cow/heifer which is expected to develop ketosis.

Kexxtone is a controlled-release formulation of monensin sodium in tablet form which is enclosed in a polypropylene delivery device. Twelve tablets are stacked in the device's plastic barrel which is equipped with retaining plastic wings. This type of presentation for cattle is often referred to as a bolus and this terminology is also used in this document. The plastic barrel has an orifice through which the tablets are exposed to moisture in the rumen. Once in the rumen, the tablets absorb water through the orifice, forming a soft gel which is then extruded through the orifice by the action of a spring which ensures the tablets are pushed to the orifice to achieve continued release throughout the 'payout period'. The device is intended to be retained in the rumen for at least the duration of the approximately 95-day payout period; however, if the wings become detached from the barrel in the rumen, the device is regurgitated.

Following shortcomings in the quality of Kexxtone leading to events of regurgitation of the device whilst still containing monensin tablets, and the increase of related adverse events reported in non-target species (dogs) for this VMP, a quality defect procedure was initiated. Within this procedure the following concerns were raised:

- a) Failures in the scheduled release of the tablets from the device to the treated animals raise doubts as to whether the treated animals receive the right dose; sub-optimal dosing could, in turn, raise questions as to the efficacy of the VMP. Reports of lack of efficacy have been received under pharmacovigilance.
- b) Regurgitation of devices that still contain monensin tablets can lead to the exposure of other animal species to the VMP. The deaths of 31 dogs have been reported in 2023 as being linked to the exposure of the dogs to regurgitated devices of Kexxtone.

The MAH of Kexxtone claimed that the quality problems were limited to certain batches manufactured in the 'focus period' (July-November 2021) and indicated that it has withheld 57 batches from that period. However, it is unclear how many batches manufactured during that period have been released, as well as the reason why the MAH decided to only block batches manufactured during that period, in spite of the fact that all of the batches technically met the specifications set forth in the marketing authorisation.

Furthermore, the MAH made some adjustments to manufacturing parameters of the finished product within the ranges approved in the process validation, implemented in March 2022 and November 2023, to address the quality defects identified (failures in the scheduled release of the monensin tablets from the device). Consequently, no variation application(s) to amend the manufacturing and control methods or the current specifications were submitted by the MAH for those changes.

Batches other than those manufactured within the focus period have been involved in the reported adverse events linked to the quality defects. Moreover, the number of adverse events reported (linked to "regurgitation", "movement of implant", "lack of efficacy" or "product defect") increased in the course of 2023 and this trend continued during the first months of 2024.

Based on all the above, the European Commission (EC) considered that it did not seem plausible to conclude that the adjustments in the manufacturing process introduced in March 2022 and November 2023 have been able to satisfactorily resolve the quality problems identified.

Therefore, on 14 March 2024 the EC submitted a request to the Committee for Veterinary Medicinal Products (CVMP) to initiate a procedure under Article 130(4) of Regulation (EU) 2019/6 for the centrally authorised VMP Kexxtone 32.4 g continuous-release intraruminal device for cattle.

The CVMP was requested to give a scientific opinion on whether:

- the benefit-risk balance for Kexxtone continues to be positive under the current terms of the marketing authorisation, including aspects of manufacturing and control contained in the dossier;
- the batches of Kexxtone that have been released on the market pose a risk to animal health or the environment and thus whether the MAH should be ordered to recall those batches;
- the MAH should implement specific measures/actions to ensure the positive benefit-risk balance for Kexxtone. In the affirmative, such measures/actions should be identified.

On 29 March 2024, the MAH notified the Agency that, following the procedure where this matter was initially being assessed within the framework for quality defects, and pending the outcome of the Article 130(4) procedure, they had proactively paused the marketing of Kexxtone in the EU.

Within the Article 130(4) procedure, the MAH was invited to provide an oral explanation to the CVMP on 16 April 2024. The CVMP considered all available data provided by the MAH in writing and within the oral explanation. A summary of the most relevant information is included below.

2. Scientific evaluation

Quality defects for Kexxtone have led to regurgitation of the device whilst still containing monensin tablets. In turn, such events raise concerns regarding efficacy in the target species cattle and the exposure of other animal species to the VMP (adverse events in the non-target species dogs have been reported).

1. Quality aspects

An investigation focusing on the quality of batches produced between July and November 2021 was initiated by the MAH who confirmed to have identified the potential root cause as changes in the manufacturing.

The MAH made some adjustments to the manufacturing parameters to address the quality defects identified. In particular, a change was implemented in routine production of the finished product in March 2022, and a further change was introduced in November 2023 which are described below.

However, despite the introduction of these process changes, batches manufactured after March 2022 have also been involved in reported adverse events. Therefore, the changes introduced to date have not been effective and a number of additional corrective and preventive actions (CAPAs), which will require variations to the marketing authorisation, have been proposed by the MAH in the context of this procedure but have not yet been implemented. These are:

- Register specific changes in the granulation process.
- Implement specific additional in-process controls on the active substance and granules before tableting.

- Revert to the previous active substance manufacturing process by reverting two changes made in the manufacturing process of the active substance. One of these changes has been identified by the MAH to be the root cause of the incomplete tablet payout *in-vivo*.
- Add the mould number to the top of the barrel to improve traceability and enable batch identification of the regurgitated barrel in the absence of its wings.
- Improve mould and wing design to reduce instances of regurgitation.
- Develop a discriminatory method for finished product to distinguish between batches of acceptable and unacceptable quality.

Discussion

In the context of this procedure, the MAH indicated that it considers one of the changes introduced in the active substance manufacturing process in May 2021 as the root cause for the incomplete tablet payout product defect ("identified quality problem"). According to the MAH, this change resulted in shifts in the Kexxtone micronisation and granulation processes.

In March 2022, changes were made to the granulator equipment settings. A further process change was introduced in November 2023 in the granulation process. These changes were not submitted as variations to the marketing authorisation as the MAH considered that they were within the approved ranges for the VMP in line with the approved process validation.

According to the MAH, process monitoring before and after the change introduced in the granulation process in November 2023 showed changes in the granules, which, in the MAH's view, improve their quality and ensure appropriate product payout *in-vivo*. An additional in-process control to include a specification for the granules is one of the proposed CAPAs by the MAH.

The gel extrusion test included on the release specification for Kexxtone has now been demonstrated to be incapable of distinguishing batches with acceptable and unacceptable tablet payout *in-vivo*. During the oral explanation, the MAH committed to develop a discriminatory method for finished product to distinguish between batches of acceptable and unacceptable quality. This test is currently under development and it was not possible for the MAH to provide an exact timeframe for its finalisation. Until such a method is developed and validated, the MAH proposed to use another test to predict acceptable tablet payout which has been used during product development and during manufacturing changes. However, the method has not been authorised as part of the marketing authorisation, is not validated and no acceptance criteria are established. The method is used for comparative purposes only.

For the additional in-process-control limits on active substance and the granules, the MAH committed to submit a variation.

The proposed CAPA to improve traceability of the VMP in the field in case of regurgitation is pending implementation of a marking system for the barrel of the device in order that the information is retained even if both wings become detached. The MAH proposed to submit a variation application.

The proposed CAPA to improve the wing design to increase its durability is proposed as a mitigation measure to reduce the incidence of regurgitation. A variation submission was proposed by the MAH.

During the oral explanation, the MAH also indicated that it intends to immediately revert to the previous active substance manufacturing process and revalidate the finished product manufacturing process. The timeframe for this CAPA is unclear.

Summary and conclusions

In the context of this procedure, the MAH indicated that it considers one of the changes introduced in the active substance manufacturing process in May 2021 to be the root cause for the incomplete payout product defect. However, in light of the multiple changes that have taken place in the manufacturing process thereafter and the multiple factors that may have contributed to the identified quality problems, the CVMP considered that the MAH should provide further evidence to confirm the underlying cause of the incomplete tablet payout.

Several CAPAs were proposed by the MAH to address the identified quality problems and only a small number of these have been implemented to date. The Committee considered that the evidence provided is not sufficient to demonstrate that these CAPAs are able to address the identified quality problems and noted that batches manufactured after implementation of some of these CAPAs have been the subject of pharmacovigilance reports. Moreover, the implementation of the proposed CAPAs would require further assessment under a variation procedure. As the remaining CAPAs are yet to be implemented, the CVMP considered that it is not possible to conclude on their ability to ensure that batches of appropriate quality will be produced.

All batches that have been the subject of adverse event reports have passed all in-process controls and finished product release tests. This shows that the controls in place are not adequate to ensure the uniformity of important product quality characteristics, which in turn ensure that the VMP has a satisfactory and uniform performance in clinical use.

The current in-process controls and product specifications are not discriminatory enough and there is currently no test available that will demonstrate the effectiveness of the CAPAs or distinguish between batches of acceptable and unacceptable quality with respect to tablet payout *in-vivo*. The MAH's proposal to temporarily use an unvalidated test, without defined test conditions and acceptance criteria, until a discriminatory finished product method is developed and validated, is not considered appropriate to confirm that batches will be of acceptable quality.

In addition, other mitigation measures to reduce the incidence of regurgitation and improve traceability are also outstanding.

2. Safety aspects

The active substance of Kexxtone (monensin) is toxic for dogs. The most common effects of monensin in dogs are anorexia, vomiting, muscle weakness, ataxia, progressive paresis/paralysis, recumbency, arrhythmias, seizures and death. The exact mechanism of toxicity in dogs is unknown.

The regurgitation of boluses containing monensin tablets as a result of this quality defect poses an increased risk of intoxication for non-target species (particularly dogs). This increased risk appears to be confirmed by the increased reporting of adverse events (including fatalities) in dogs in 2023/2024 (based on data in the data warehouse), linked to the exposure of dogs to regurgitated devices of Kexxtone.

Discussion

In August 2022, the MAH submitted a signal in the Pharmacovigilance database, reporting 21 cases (including 8 fatalities) in dogs during the period 1 August 2020 to 15 June 2022. In this period the clinical signs for dogs were elevated liver enzymes, paresis and collapse. The conclusion of the MAH was to continue monitoring the canine exposure.

The latest signal submission to the Pharmacovigilance database was on 31 January 2024, but no exposure to dogs was mentioned. However, 54 new cases concerning intoxication in dogs have been

received between January 2023 and March 2024 (47 of them in 2023), according to data warehouse analysis. These cases received in 2023 and the first months of 2024 stated that dogs ate an unknown amount of monensin, and involved 40 deaths in dogs.

The CVMP noted the existing risk mitigation measures: warnings in the summary of product characteristics and package leaflet; educational programs and materials for veterinarians and farmers in EU countries; embossed description of the active substance monensin on the device; continuous improvement and stewardship of the device design and its properties to minimise regurgitation related to device failure; active method development for a finished product discriminatory method to ensure appropriate tablet payout *in-vivo* and thus minimising potential non-target species exposure. However, despite those measures there has been an increase in reported cases of adverse events in dogs in 2023 which continues in 2024.

The MAH was of the opinion that pharmacovigilance data indicates that the increased reporting of regurgitation is correlated to the increase in quality defect reports of incomplete tablet payout but are not reflective of an actual increase in the rate of regurgitation and therefore the risk to dogs has not increased as a result of incomplete tablet payout.

In order to supplement already existing risk mitigation measures, the MAH proposed to increase label warnings on the product packaging regarding non-target species exposure, to emboss an additional warning for dogs on each individual barrel and to explore the possibility of incorporating a bitterant in the capsule to deter non-target species consumption. The MAH also proposed an additional EU-wide educational campaign on barrel disposal and non-target species exposure avoidance and farm hazards in general.

Summary and conclusions

The CVMP considered that the correlation between regurgitated devices with incomplete tablet payout and the increased reporting of adverse events in non-target species (dogs) since the quality defect was recorded was indicative of an increased risk of intoxication for other animals than the target species.

The MAH's assertion that there is no increased risk to non-target species is not consistent with available pharmacovigilance data. Indeed, according to the information provided by the MAH, the number of reports of regurgitation or movement of implant associated with incomplete tablet payout (i.e., boluses containing monensin tablets after 95 days) appears to have increased during the course of 2023. Furthermore, even if it was accepted that the overall frequency of regurgitation of boluses has not increased (but rather the reporting of them has, due to the presence of monensin tablets), it was considered that the risk to non-target species has increased as a result of this quality defect due to the higher number of regurgitated boluses containing monensin tablets reported.

The Committee noted that although the MAH claimed to have made some adjustments to manufacturing parameters to address the quality defects identified and implemented these adjustments since March 2022, the fact remains that reporting of intoxication (including fatalities) in dogs increased in 2023 and continues in 2024, and includes batches manufactured since March 2022, suggesting that an increased risk for non-target species continues, notwithstanding the risk mitigation measures implemented to date.

The CVMP also noted that already implemented measures to minimise non-target species exposure to Kexxtone have not been able to satisfactorily address the risk of adverse events in the non-target species dogs. With regard to the MAH's proposal to supplement existing risk mitigation label warnings on the product packaging regarding non-target species exposure and to emboss an additional warning on each barrel, the CVMP considered that they would not be able to adequately address the increased risk posed by regurgitated boluses containing monensin tablets. The MAH's proposal to explore the possibility of incorporating a bitterant in the device is considered worthy of pursuing; however, as this

is only being explored, it cannot be considered at this point as an adequate measure to address the identified risks to non-target species.

3. Efficacy aspects

The identified quality problems discussed above have led to regurgitation of the device whilst still containing monensin tablets which results in the treated animals not receiving the full amount of monensin for the intended duration, hence in sub-optimal dosing. As a consequence, this raises questions as to the efficacy of the VMP. Reports of lack of efficacy have been received under pharmacovigilance.

Discussion

The MAH submitted a signal to the Pharmacovigilance database on 31 January 2024 assessing signs of “lack of efficacy” and “regurgitation” in relation to cases associated with incomplete tablet payout of monensin tablets from the device. Reports of “movement of implant” have also been taken into account.

The signal report included the cases reported in EudraVigilance Veterinary during the year 2023 and also the cumulative number of cases since the first marketing of the VMP. From 1 January to 31 December 2023, 81 cases of ‘lack of efficacy’, 493 cases of ‘movement of implant’ (326 of which were associated with incomplete tablet payout) and 338 cases of ‘regurgitation’ (236 of which were associated with incomplete tablet payout) were reported. These reports during 2023 account for 65%, 78% and 82%, respectively, of all reports for the respective signs recorded to date, suggesting a significant increase in the incidence of such reports in 2023 compared to previous years.

During the assessment of the 8th PSUR in 2021, the MAH discussed the replacement of the device material with a higher strain-to-break material. The change of this material was due to the cessation of the polypropylene manufacturing by the supplier. However, the MAH stated that a decrease in wing breakage, and therefore a reduction in the incidence of regurgitations, would be expected and the MAH committed to assess the impact of this change by continuing to monitor reports of regurgitation. Given that regurgitated boluses (with incomplete tablet payout) have been reported as being associated with this quality defect, it was unclear as to the impact (if any) the change in device material has had, or the extent to which broken wings contribute to the regurgitation of boluses. Therefore, the MAH was requested to provide an update on this matter within the oral explanation at the CVMP meeting in April 2024. The MAH confirmed that the change to a higher strain-to-break material did not correlate to any trends in product defects and/or regurgitation events, as monitored from its implementation in 2020.

Due to the nature of this VMP, i.e. a continuous release-device, failure to release the active substance as intended over a period of approximately 95 days raises concerns as to whether treated animals receive the necessary dose of monensin. The relationship between regurgitated devices with incomplete tablet payout and an increased reporting of ‘lack of efficacy’ since 2021 is indicative of an increased risk of incomplete and sub-optimal dose administration, and in turn casts doubts on the efficacy of the VMP for the intended use. Having administered the VMP, users will expect the product to remain in-situ and deliver monensin to the treated animal for approximately 95 days, thereby reducing the incidence of ketosis in peri-parturient dairy cows and heifers expected to develop ketosis. Incomplete payout of monensin due to regurgitation of boluses containing monensin tablets inherently presents a risk to the treated animals in terms of sub-optimal/incomplete dose delivery.

The MAH considered that, although there had been a number of reports of suspected lack of efficacy, few included adequate information to confirm that clinical ketosis had developed in treated animals and many reports assumed that there was a lack of efficacy due to the presence of monensin tablets in

regurgitated boluses. Whilst acknowledging that pharmacovigilance reports may not always contain sufficient information to elucidate whether the reported “lack of efficacy” has been confirmed in practice, the fact remains that, where the bolus is regurgitated whilst still containing monensin tablets, the intended dose has not been delivered to the treated animal and therefore the amount of monensin that is administered to the treated animal is less than the dose on the basis of which efficacy was demonstrated when the marketing authorisation was granted. In these circumstances, the efficacy of the VMP cannot be assumed.

In response to the questions asked in the course of the investigation of this quality defect, the MAH provided the following information:

2023	Jan-Mar		Apr-Jun		Jul-Sep		Oct-Dec		Jan-Dec	
SIGN	Case count	Incomplete payout	Case count	Incomplete payout	Case count	Incomplete payout	Case count	Incomplete payout	Case count	Incomplete payout
Regurgitation	73	49	69	46	81	62	115	79	338	236
Movement of implant	109	59	116	79	113	82	155	106	493	326
Regurgitation or Movement of implant	111	60	120	81	117	85	156	106	504	332
Product defect*	5	4	3	2	15	13	146	102	169	121
As submitted in IRIS		63		77		87		112		339

*No cases coded Product defect without other sign Movement of implant or Regurgitation

This table shows the “regurgitation”, “movement of implant” and “product defect” cases in relation to incomplete tablet payout issue for the year 2023, separated into quarters. It can be seen that a large number of the cases reported during 2023 with the above-mentioned signs also show product release problems.

Summary and conclusion

Given the increase in pharmacovigilance reports supporting lack of efficacy of Kexxtone since the quality defect was reported, and the significant increase in the regurgitation of boluses with incomplete payout of tablets during 2023 (and which continues into 2024), the CVMP concluded that serious concerns arise in respect of the efficacy of this VMP.

The CVMP considered that failure to release all of the intended dose of monensin over the anticipated dosing period (approximately 95 days) puts into question the efficacy of the VMP. The Committee also concluded that, as the MAH cannot guarantee that the identified quality problems are not present in the batches currently on the market, the efficacy of the batches of Kexxtone currently marketed is compromised.

Benefit-risk balance assessment

Within this procedure, the MAH was requested to clarify whether the benefit-risk balance for Kexxtone continues to be positive and whether the batches currently marketed and being released to the market may be considered to pose a risk to animal health or the environment.

During the oral explanation held in April 2024, the MAH pointed out that Kexxtone is the only marketed VMP specifically indicated for the reduction in the incidence of ketosis. However, the Committee considered that there are other measures to prevent ketosis, such as ensuring good feed intake and diets that provide the necessary nutrients during the late dry period or immediately after calving. There are also alternatives on the market for both prevention and treatment of ketosis in the cow.

In addition, it is important to note that the Medicine Shortages Single Point of Contact (SPOC) Working Party at EMA assessed the criticality of the potential shortage of Kexxtone in the European Union. Although not all EU/EEA NCAs for veterinary medicines are represented in the SPOC WP (21 National Competent Authorities (NCAs)), 15 NCAs responded to the survey and none of them would consider a shortage of this VMP to be critical. Moreover, they indicated the availability of alternatives for managing ketosis in cattle. Based on the feedback received, it was considered that there would not be a critical impact on the EU/EEA Member States in case shortages of Kexxtone occur.

After considering all clarifications provided by the MAH as described in the sections above, the CVMP concluded that the identified quality problems compromise the efficacy of Kexxtone by hindering the ability of the treated cattle to receive the dosage of monensin on the basis of which efficacy was established when the marketing authorisation was granted. Furthermore, those quality problems have led to the exposure of non-target species to the active substance monensin, which in turn has led to toxicities and fatal outcomes in dogs. Overall, the CVMP concluded that the benefit-risk balance of Kexxtone 32.4 g continuous-release intraruminal device for cattle is no longer positive until the concerns highlighted as a result of the identified quality problems have been satisfactorily addressed.

It is important to note that the CVMP duly considered the MAH's proposal in the context of this procedure to recall only batches manufactured between July 2021 and March 2022 but concluded that it would be insufficient for the following reasons:

- The MAH indicated that the implementation of the change to the active substance manufacturing process in May 2021 is the root cause for the incomplete tablet payout. If the proposition of the MAH as to the root cause is correct, it would not be possible to have confidence on the quality of the batches released until when the change is reverted.
- The manufacturing changes introduced in the finished product in March 2022 and November 2023 were not sufficient to address the incomplete payout problem. This is further confirmed by the fact that at least 24 batches manufactured between March and August 2022 are involved in similar adverse events reported.

Grounds for suspension of the marketing authorisations

Whereas

- The CVMP considered the procedure initiated under Article 130(4) of Regulation (EU) 2019/6 for Kexxtone 32.4 g continuous-release intraruminal device for cattle (monensin).
- The CVMP noted that the identified quality problems for Kexxtone lead to the regurgitation of the device whilst still containing monensin tablets.
- The CVMP reviewed the totality of the available data, including data provided by the marketing authorisation holder in writing and in an oral explanation on the quality deficiencies of Kexxtone, on the potential lack of efficacy in cattle, on adverse events in the non-target species dogs, and on the overall benefit-risk balance of the VMP.
- The CVMP noted that there is currently no validated method that can distinguish between batches of acceptable and unacceptable quality with respect to tablet payout in-vivo.

- The CVMP noted that whilst some corrective and preventive actions (CAPAs) have been implemented in the manufacturing process, the effectiveness of these measures in addressing the incomplete tablet payout has not been adequately demonstrated and is not borne out given the continued pharmacovigilance reports for batches manufactured after their implementation.
- The CVMP also noted that variation procedures to implement some of the identified CAPAs have not yet been initiated by the MAH.
- The CVMP considered that the evidence on the risk of increased exposure of the non-target species dogs to regurgitated devices still containing undissolved tablets raised serious safety concerns. Serious adverse events in dogs, including fatalities, continue being reported. In 2023, thirty-one deaths in dogs were reported and in the first 3 months of 2024, nine deaths in dogs were reported.
- The CVMP noted all risk mitigation measures proposed by the MAH and concluded that the already implemented measures have not been able to satisfactorily address the risk of adverse events in the non-target species dogs and the additional measures proposed cannot be implemented immediately against this risk.
- The CVMP noted an increase of pharmacovigilance reports supporting lack of efficacy of Kexxtone and an increased number of regurgitated boluses containing monensin tablets. Failures in the scheduled release of the tablets from the device to the treated cattle have a negative impact on the ability of the treated animals to receive the right dose of monensin with regard to the indication of the VMP and the treatment period as foreseen in the marketing authorisation, compromising the efficacy of the VMP.

In view of the above, the CVMP concluded that, until the concerns highlighted as a result of the identified quality problems have been satisfactorily addressed, the benefit-risk balance of Kexxtone 32.4 g continuous-release intraruminal device for cattle is no longer positive.

Therefore, the CVMP recommended the suspension of the marketing authorisation for Kexxtone (EU/2/12/145/001-003).

In addition, as a precautionary measure to prevent further exposure and thereby minimise the risk of further serious adverse events, the CVMP considered that in view of the estimated amount of veterinary medicinal product available within the distribution chain, all batches of this VMP should be recalled from the market at all levels of the distribution chain - wholesale, retail and user (veterinarians/farmers).

Furthermore, the CVMP recommended that the MAH should present a topic-specific communication plan and a direct animal healthcare professional communication to be disseminated to inform veterinarians and other animal healthcare professionals of the suspension of the marketing authorisation. This is in line with the guidance on veterinary good pharmacovigilance practice¹ and the documents should be presented to the CVMP for adoption during the May 2024 CVMP meeting.

For the suspension of the marketing authorisation for Kexxtone to be lifted, the MAH should satisfactorily address the conditions detailed below and provide robust scientific evidence on a positive benefit-risk balance of the VMP.

¹ Guideline on veterinary good pharmacovigilance practices (VGVP). Module: veterinary pharmacovigilance communication ([EMA/63454/2021](#))

Annex II

Conditions for lifting the suspension of the marketing authorisation

Conditions for lifting the suspension of the marketing authorisation

For the suspension of the marketing authorisation to be lifted for Kexxtone 32.4 g continuous-release intraruminal device for cattle, the marketing authorisation holder (MAH) shall provide robust scientific evidence on a positive benefit-risk balance of the veterinary medicinal product.

The following conditions should be fulfilled by the MAH:

1. the underlying cause of the incomplete tablet payout should be further confirmed and appropriate corrective and preventive actions (CAPAs) should be applied to address it, which should include at least the following:
 - a. develop a discriminatory method for the release of the finished product that can distinguish between batches of acceptable and unacceptable quality with respect to tablet payout *in-vivo* and add this new test to the release specification.
 - b. implement specific additional in-process controls on the active substance and granules before tableting and any other process controls identified as critical to control payout *in-vivo*.
 - c. define specific changes in the granulation process and adjust the in-process control.
2. take appropriate measures to ensure that future manufactured barrels are readily identifiable, even if both wings are removed.
3. present a communication strategy to raise awareness of risks posed to non-target species from regurgitated boluses containing monensin tablets.

It is recommended that the marketing authorisation be suspended until all conditions are satisfactorily addressed. Relevant variation application(s) should be submitted for the above-mentioned conditions – where required.