Annex I

List of the names, pharmaceutical form, strength of the veterinary medicinal products, animal species, route of administration, marketing authorisation holder in the Member States

Member State (EU/EEA)	Marketing authorisation holder	Product name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Austria	Norbrook Laboratories Ltd Station Works, Newry, BT35 6JP Northern Ireland	Closamectin 5mg/ml + 200mg/ml Pour- On Lösung für Rinder	Ivermectin Closantel	5mg/ml 200mg/ml	Pour-On solution	Cattle	Topical use
Belgium	Norbrook Laboratories Ltd Station Works, Newry, BT35 6JP Northern Ireland	Closamectin 5mg/ml + 200 mg/ml pour-on oplossing voor rundvee	Ivermectin Closantel	5mg/ml 200mg/ml	Pour-On solution	Cattle	Topical use
Czech Republic	Norbrook Laboratories Ltd Station Works, Newry, BT35 6JP Northern Ireland	Closamectin 5mg/ml + 200mg/ml roztok pro nalévání na hřbet - pour-on	Ivermectin Closantel	5mg/ml 200mg/ml	Pour-On solution	Cattle	Topical use
Denmark	Norbrook Laboratories Ltd Station Works, Newry, BT35 6JP Northern Ireland	Closamectin Pour-On	Ivermectin Closantel	5mg/ml 200mg/ml	Pour-On solution	Cattle	Topical use
France	Norbrook Laboratories Ltd Station Works, Newry, BT35 6JP Northern Ireland	CLOSAMECTIN POUR-ON SOLUTION POUR BOVINS	Ivermectin Closantel	5mg/ml 200mg/ml	Pour-On solution	Cattle	Topical use

Member State (EU/EEA)	Marketing authorisation holder	Product name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Germany	Norbrook Laboratories Ltd Station Works, Newry, BT35 6JP Northern Ireland	Closamectin 5mg/ml + 200mg/ml Pour- On Lösung zum Übergießen für Rinder	Ivermectin Closantel	5mg/ml 200mg/ml	Pour-On solution	Cattle	Topical use
Greece	Norbrook Laboratories Ltd Station Works, Newry, BT35 6JP Northern Ireland	Closamectin 5mg/ml + 200mg/ml διάλυμα επίχυσης για Βοοειδή	Ivermectin Closantel	5mg/ml 200mg/ml	Pour-On solution	Cattle	Topical use
Ireland	Norbrook Laboratories Ltd Station Works, Newry, BT35 6JP Northern Ireland	Closamectin 5mg/ml + 200 mg/ml Pour-On Solution for Cattle	Ivermectin Closantel	5mg/ml 200mg/ml	Pour-On solution	Cattle	Topical use
Ireland	Norbrook Laboratories Ltd Station Works, Newry, BT35 6JP Northern Ireland	Closivet Pour-On Solution for Cattle	Ivermectin Closantel	5mg/ml 200mg/ml	Pour-On solution	Cattle	Topical use
Italy	Norbrook Laboratories Ltd Station Works, Newry, BT35 6JP Northern Ireland	Closamectin 5mg/ml + 200 mg/ml Soluzione Pour-On per bovini	Ivermectin Closantel	5mg/ml 200mg/ml	Pour-On solution	Cattle	Topical use

Member State (EU/EEA)	Marketing authorisation holder	Product name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Italy	Norbrook Laboratories Ltd Station Works, Newry, BT35 6JP Northern Ireland	Vermax Pour-On 5mg/ml + 200mg/ml Soluzione Pour-On per bovini	Ivermectin Closantel	5mg/ml 200mg/ml	Pour-On solution	Cattle	Topical use
Poland	Norbrook Laboratories Ltd Station Works, Newry, BT35 6JP Northern Ireland	Closamectin Pour-On 5 mg/ml + 200 mg/ml, roztwór do polewania dla bydła	Ivermectin Closantel	5mg/ml 200mg/ml	Pour-On solution	Cattle	Topical use
Portugal	Norbrook Laboratories Ltd Station Works, Newry, BT35 6JP Northern Ireland	Closamectin FF 5 mg/ml + 200mg/ml solução para unção contínua para bovinos	Ivermectin Closantel	5mg/ml 200mg/ml	Pour-On solution	Cattle	Topical use
Romania	Norbrook Laboratories Ltd Station Works, Newry, BT35 6JP Northern Ireland	Closamectin 5mg/ml + 200 mg/ml Soluţie Pour-On pentru bovine	Ivermectin Closantel	5mg/ml 200mg/ml	Pour-On solution	Cattle	Topical use
Spain	Norbrook Laboratories Ltd Station Works, Newry, BT35 6JP Northern Ireland	CLOSAMECTIN 5 mg/ml + 200 mg/ml SOLUCION POUR-ON PARA BOVINO	Ivermectin Closantel	5mg/ml 200mg/ml	Pour-On solution	Cattle	Topical use

Member State (EU/EEA)	Marketing authorisation holder	Product name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Spain	Norbrook Laboratories Ltd Station Works, Newry, BT35 6JP Northern Ireland	Closivet Solución Pour- On	Ivermectin Closantel	5mg/ml 200mg/ml	Pour-On solution	Cattle	Topical use
Sweden	Norbrook Laboratories Ltd Station Works, Newry, BT35 6JP Northern Ireland	Closamectin vet 5 mg/ml+200 mg/ml Pour-on lösning till nöt	Ivermectin Closantel	5mg/ml 200mg/ml	Pour-On solution	Cattle	Topical use
Slovenia	Norbrook Laboratories Ltd Station Works, Newry, BT35 6JP Northern Ireland	Closamectin 5mg/ml + 200mg/ml Pour- On kožni poliv, raztopina za govedo	Ivermectin Closantel	5mg/ml 200mg/ml	Pour-On solution	Cattle	Topical use
Slovakia	Norbrook Laboratories Ltd Station Works, Newry, BT35 6JP Northern Ireland	Closamectin 5mg/ml + 200mg/ml pour- on roztok pre hovädzí dobytok	Ivermectin Closantel	5mg/ml 200mg/ml	Pour-On solution	Cattle	Topical use
United Kingdom	Norbrook Laboratories Ltd Station Works, Newry, BT35 6JP Northern Ireland	Closamectin 5mg/ml + 200 mg/ml Pour-on Solution for Cattle	Ivermectin Closantel	5mg/ml 200mg/ml	Pour-On solution	Cattle	Topical use

Member State (EU/EEA)	Marketing authorisation holder	Product name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
United Kingdom	Norbrook Laboratories Ltd Station Works, Newry, BT35 6JP Northern Ireland	Closiver 5mg/ml + 200mg/ml Pour-On Solution for Cattle	Ivermectin Closantel	5mg/ml 200mg/ml	Pour-On solution	Cattle	Topical use
United Kingdom	Norbrook Laboratories Ltd Station Works, Newry, BT35 6JP Northern Ireland	Norofas Pour-On Solution for Cattle	Ivermectin Closantel	5mg/ml 200mg/ml	Pour-On solution	Cattle	Topical use

Annex II

Scientific conclusions and grounds for amendment of the summary of product characteristics and package leaflet

Overall summary of the scientific evaluation of Closamectin Pour-On Solution and associated names (*see Annex I*)

1. Introduction

CLOSAMECTIN POUR-ON SOLUTION POUR BOVINS is a veterinary medicinal product which has been authorised in France since 25 May 2011 following a decentralised procedure (DCP) (UK/V/0369/001) with the United Kingdom (UK) as reference Member State. The product is effective for use in cattle for the treatment of mixed trematode (fluke) and nematode or arthropod infestations due to roundworms, lungworms, eyeworms, warbles, mites and lice.

Closamectin Pour-On Solution should be administered topically at a dose of 500 mg ivermectin per kg body weight and 20 mg closantel per kg body weight (1 mL per 10 kg body weight). The product should not be re-applied (within 7 weeks) to cattle.

Other veterinary medicinal products with the same qualitative and quantitative composition which belong to the same marketing authorisation holder (MAH), Norbrook Laboratories Ltd, are also authorised under two other DCP and three national procedures, as follows:

- UK/V/0325/001 – Closamectin Pour-On (UK, Ireland);
- UK/V/0368/001 – Closiver 5mg/ml & 200 mg/ml Pour-On (UK); Closamectin 5mg/ml & 200 mg/ml Pour-On (Austria, Belgium, Czech Republic, Denmark, Germany, Greece, Italy, Poland, Portugal, Romania, Slovakia, Slovenia, Spain and Sweden);
- Closivet Pour-On Solution for Cattle (Ireland);
- Closivet Solución Pour-On (Spain); and
- Vermax Pour-On 5mg/ml & 200 mg/ml Soluzione Pour-On per bovini (Italy).

On 19 June 2015, ANMV circulated a rapid alert notifying Member States, the European Commission and the European Medicines Agency of the intention to suspend the marketing authorisation for CLOSAMECTIN POUR-ON SOLUTION POUR BOVINS in France, following the evaluation of pharmacovigilance data. The ANMV received a total of 123 adverse event reports involving CLOSAMECTIN POUR-ON POUR BOVINS between 25 May 2011 and 31 May 2015 in which 401 animals were affected and 121 died. The adverse events principally related to neurological signs (ataxia, recumbency, paresis/paralysis and blindness) and/or gastrointestinal disorders (diarrhoea, anorexia etc.) some of which had a fatal outcome. The nature of the reported clinical signs was considered by ANMV to be indicative of the clinical signs associated with overdose toxicity of closantel. Although the overall incidence of adverse events was considered to be within acceptable limits (0.006% in the last annual periodic safety update report (PSUR)) the continued occurrence of serious adverse events and the severity of subsequent losses on farms in France were considered significant, which led to the suspension of the marketing authorisation in France on 6 July 2015. The product was also recalled at veterinary clinic and wholesale level.

The aforementioned products have the same qualitative and quantitative composition and consequently it was considered that the animal health issues described were applicable to these products as well.

2. Discussion of data available

To investigate the potential relation between the adverse events observed and Closamectin Pour-On Solution and associated names, the CVMP considered the data provided by the MAH, Norbrook

Laboratories Ltd. This included a review of scientific literature regarding the pharmacology and toxicology of ivermectin and closantel, cumulative pharmacovigilance experience following use of the products in the European Union (EU) since 2009, a comparison with ivermectin-based products and with ivermectin/closantel injectable formulations held by the MAH, investigations carried out by the MAH to identify possible factors involved in reported adverse events and proposals for risk mitigation measures and actions.

In addition to the pharmacovigilance data provided by the MAH, where available, results of the diagnostic tests (e.g. blood tests and post-mortem examinations etc.) to investigate the adverse events were also provided. The CVMP considered the clinical signs in the reported adverse events were similar to those observed with closantel overdose toxicity, although this could not be confirmed definitively as post-mortems were not conducted for all fatal events. It was noted that in general the product was reported to have been administered at the recommended dose. It was hypothesised that licking behaviour may contribute to the overexposure leading to closantel toxicity in some of the animals observed where the correct dose had been applied although this has not been confirmed definitively.

The CVMP also reviewed the data submitted to gain the marketing authorisation for the pour-on combination products, focusing in particular on the target animal safety studies and toxicity events from the studies and in published literature. Pre-marketing studies tended to suggest that both combined ivermectin/closantel and closantel only formulations were well tolerated in cattle at doses up to 3 times the recommended posology, even in case of repeated administration. Additionally, observations made on the consequences of licking/grooming behaviour suggested that the maximal dose administered orally did not seem to produce any adverse effect. From the literature review reported it appeared that variability existed between animals in terms of their clinical response to a same level of overdose. This may suggest that risk factors exist in the field, leading to either overexposure of some animals to closantel or enhanced intrinsic sensitivity of these animals to the toxic effects of closantel.

A comparative review of the safety profile in cattle of other products containing ivermectin and/or closantel held by the MAH (including the injectable combination product) was conducted. The CVMP considered the clinical profile of injectable and pour-on combined formulations to be comparable, except for signs of blindness/impaired vision (reported only with the pour-on products) and application site and respiratory signs (reported only with the injectable product). It was also noted that the overall adverse reaction incidence was slightly higher for the injectable combination product when compared to the pour-on products; with, on average, a higher number of animals involved in each report although the reported mortality incidence was lower. Although the pharmacovigilance reports indicated potential closantel toxicity as an underlying cause, it was noted that reports of neurological events (including a case of blindness) and diarrhoea occurred with the ivermectin-only formulations. Therefore, it was considered difficult to ascertain whether the clinical signs observed indicative of toxicity may be due to the ivermectin and/or the closantel components of the combination product Closamectin Pour-On.

The CVMP considered the additional data relating to the adverse event reports provided by the MAH to investigate potential risk factors associated with the adverse events in animals and possible explanations for the higher incidence of fatal adverse events reported in France compared with other EU Member States. The data reviewed did not indicate age, sex, breed or geographical distribution as potential risk factors for the adverse events observed. It was however, suggested that licking/grooming, possibly associated with the predominantly beef cattle breeding systems in France could explain, in part, the comparatively higher number of events reported there. However, there is no evidence to date to support this hypothesis.

Additional investigations were initiated in animals affected in 2015, involving monitoring vitamins A, E and selenium blood levels in samples from both affected and unaffected animals. These deficiencies and poor nutritional status in general were considered potential factors associated with the adverse events observed following treatment and considered possible explanations for the higher frequency of reported adverse events in France. However further investigations were considered necessary to confirm or refute nutritional status and specific micro-nutrient deficiencies as risk factors for the adverse effects observed in animals following use of Closamectin Pour-on Solution and associated names. This follow-up should also continue to investigate other potential risk factors which may also play a role in the adverse events observed, including, for example, aspects related to animal husbandry.

The Committee considered the measures proposed by the MAH to mitigate the risk of adverse events following use of the product, which included changes to the product information detailed below. The amendments to the product information were supported as these were considered to improve the information on adverse events, reinforce surveillance in herds where adverse events occur, in light of the pharmacovigilance experience to date, and introduce precautions for treatment of animals with low nutritional status.

SPC section 4.5 Special precautions for use: Special precautions for use in animals:

> *Care should be taken when treating animals which may be of low nutritional status as this may increase susceptibility of adverse events occurring.*
>
> *SPC section 4.6 Adverse reactions (Frequency and Seriousness)*
>
> *In very rare cases (less than 1 animal in 10,000 animals, including isolated reports), neurological signs such as blindness, ataxia, and recumbency may occur after administration of the product. These cases may also be associated with gastrointestinal signs such as anorexia, diarrhoea and in extreme cases signs may persist and may result in death of the animal.*
>
> *Even though the overall incidence of adverse events is very rare, it has been noted that, when there is an adverse event in a herd, several animals may be affected. Therefore, should neurological signs be observed in one animal, it is recommended to reinforce surveillance, at the herd level, of all treated animals.*

The CVMP also considered a risk management plan proposed by the MAH detailing annual PSUR reporting for Closamectin Pour-On Solution and associated names, further detailed investigation of pharmacovigilance reports (including collection of data on treated un-affected animals within the same herd) and a proposal for 'education, training and guidance' of end users to ensure that the risks of the products and the precautions for use are fully understood. The measures detailed in the risk management plan proposed by the MAH were supported, with additional refinement described below.

The proposal for annual PSUR submissions, covering all products related to Closamectin Pour-On Solution and associated names was supported. It was emphasised that analysis and incidence calculations should be performed on the overall data however also ensuring precise identification of the concerned product for individual adverse event reports. Sales volumes should also be reported separately for specific products for each Member State. The detailed results of investigations of adverse events and their analysis should be included in each PSUR.

It was recommended that additional data be collected for the adverse events occurring in future to determine the potential role of the products, including potential closantel toxicity, and also investigate potential risk factors associated with the adverse events reported following treatment. Post-mortem analysis of fatal cases was considered necessary to determine the potential role of closantel toxicity, as well as diagnosing any other disease processes. In addition, as the link between plasma closantel and

toxicity has yet to be established it was also recommended to provide results of blood plasma sampling, together with information on the time of treatment, onset of clinical signs and sampling. Additional diagnostic analyses, including blood samples (including biochemistry and micronutrient analyses) and faecal analysis, should be conducted in the affected animals ensuring that all samples are handled appropriately to avoid the introduction of any bias into analyses. It was also recommended to ensure data collection on a representative sample of unaffected treated animals within the same herd. Information should also be collected on the affected herd and husbandry system in general, including herd health status. The detailed results of these analyses should be reported at regular intervals with every PSUR submission and immediately in case of any significant finding or upon request.

It was also proposed to provide 'education, training and guidance' to end-users to improve understanding related to the risks of the products and the precautions for use. In line with the requirements, all communication tools relating to pharmacovigilance should be submitted to the concerned NCAs, for information, before dissemination.

It was proposed that third parties involved in pharmacovigilance activities related to these products (e.g distributors) be made aware of the risk management measures proposed. This should be done before their implementation and for any future changes to the measures deemed necessary. Updates to the risk management plan detailing the risk mitigation and surveillance measures should be proposed as required as soon as any issues arise, otherwise the risk management plan should be reviewed on a yearly basis at least, in conjunction with the PSUR submission.

3. Benefit-risk assessment

Closamectin Pour-On Solution and associated names is authorised in several EU Member States. The products are effective for use in beef cattle for the treatment of mixed trematode (fluke) and nematode or arthropod infestations due to roundworms, lungworms, eyeworms, warbles, mites and lice.

As an indirect benefit, it is noted that pour-on products are often preferred over injectable products due to the ease of administration. Closantel is an alternative flukicide to triclabendazole to which resistance is emerging. Other treatment options have limited activity against immature fluke.

The principal risks associated with the product relate to the potential for adverse events involving neurological signs (ataxia, recumbency, paresis/paralysis and blindness) and/or gastrointestinal disorders (diarrhoea, anorexia etc.) in treated animals some of which have been fatal. The nature of the adverse events were indicative of the clinical signs associated with overdose toxicity of closantel although it was noted that in general affected animals were reported to have been treated according to the recommended dose.

From 2000 until 30 June 2015, a total of 371 adverse events reports were reported in the EU, 65% of which, according to the MAH, concerned animal toxicity, mainly in France (120 reports) and the UK (91 reports). The overall EU incidence of adverse events, in relation to sales volumes was classified as 'very rare' (0.003%) and considered within acceptable limits. Higher incidence values were reported in Sweden (0.011%) and France (0.007%). It was noted that these events often involved more than one animal within affected herds. The average number of affected animals per adverse event report in the EU was 3.9. It remained unclear, however, why the frequency of adverse events reported in France was higher than for other Member States and further investigations into this were initiated by the MAH.

Measures to mitigate the risk of adverse events following use of the product have been proposed. These included changes to the product information (as detailed in Annex III of the Opinion) to improve the information on adverse events, reinforce surveillance in herds where adverse events occur and

introduce precautions for treatment of animals with low nutritional status. Additionally the MAH proposed to implement a risk management plan comprising submission of annual 'combined' PSUR reports for the products concerning Closamectin Pour-On Solution and associated names (as detailed in Annex I of the Opinion); detailed investigation of future pharmacovigilance reports which should include data collection from treated un-affected animals within the same herd (including farm history and herd health status, assessment of animal health and nutritional status involving biochemistry and micronutrient analysis; investigation of potential closantel toxicity (via blood plasma sampling and post-mortem examinations); and 'education, training and guidance' for end-users to ensure that the risks of the products and the precautions for use are fully understood. These measures were considered to be appropriate to mitigate the risks observed following treatment.

Although the underlying mechanism for the adverse events has not yet been determined, the benefit-risk balance of Closamectin Pour-On Solution and associated names was considered favourable subject to amendments to product information and implementation of additional risk mitigation and surveillance measures to provide annual 'combined' PSURs, further investigate adverse events reported in future and provide 'education, training and guidance' to end-users to improve understanding related to the risks of the products and the precautions for use.

Grounds for lifting of the suspension of the marketing authorisation for CLOSAMECTIN POUR-ON SOLUTION POUR BOVINS in France and amendment of the summary of product characteristics and package leaflet

Whereas:

- on the basis of the pharmacovigilance and additional data reviewed, including risk minimisation measures, the CVMP considered that the overall benefit-risk balance is positive for the veterinary medicinal products (see Annex I) subject to amendments in the product information;

the CVMP has recommended lifting of the suspension of the marketing authorisation for CLOSAMECTIN POUR-ON SOLUTION POUR BOVINS in France; variations of the marketing authorisations for Closamectin Pour-On Solution and associated names as referred in Annex I in order to amend the summary of product characteristics and package leaflet in line with recommended changes in the product information as set out in Annex III; and conditions of the marketing authorisations as set out in Annex IV.

Annex III

Amendments in the relevant sections of the summary of product characteristics and package leaflet

Summary of Product Characteristics

Add, to all products (if not already present):

4.5 Special precautions for use

Special precautions for use in animals

……..

Care should be taken when treating animals which may be of low nutritional status as this may increase susceptibility of adverse events occurring.

4.6 Adverse reactions (frequency and seriousness)

In very rare cases (less than 1 animal in 10,000 animals, including isolated reports), neurological signs such as blindness, ataxia, and recumbency may occur after administration of the product. These cases may also be associated with gastrointestinal signs such as anorexia, diarrhoea and in extreme cases signs may persist and may result in death of the animal.

Even though the overall incidence of adverse events is very rare, it has been noted that, when there is an adverse event in a herd, several animals may be affected. Therefore, should neurological signs be observed in one animal, it is recommended to reinforce surveillance, at the herd level, of all treated animals.

Package leaflet:

Add, to all products (if not already present):

6. ADVERSE REACTIONS

In very rare cases (less than 1 animal in 10,000 animals, including isolated reports), neurological signs such as blindness, ataxia, and recumbency may occur after administration of the product. These cases may also be associated with gastrointestinal signs such as anorexia, diarrhoea and in extreme cases signs may persist and may result in death of the animal.

Even though the overall incidence of adverse events is very rare, it has been noted that, when there is an adverse event in a herd, several animals may be affected. Therefore, should neurological signs be observed in one animal, it is recommended to reinforce surveillance, at the herd level, of all treated animals.

12. SPECIAL WARNING(S)

Special precautions for use in animals:

……..

Care should be taken when treating animals which may be of low nutritional status as this may increase susceptibility of adverse events occurring.

Annex IV

Conditions of the marketing authorisations

The national competent authorities of Member State(s) or the reference Member State, as applicable, shall ensure that the following conditions are fulfilled by the marketing authorisation holder:

- implementation of a risk management plan addressing the following risk mitigation and surveillance measures:
  - annual PSUR submissions covering all concerned veterinary medicinal products (see Annex I);
  - intensified data collection relating to pharmacovigilance reports; and
  - education, training and guidance for end-users.

A single risk management plan should be presented covering all products included within the scope of this procedure. The risk management plan should be submitted to the national competent authorities within 3 months of the Commission Decision and maintained until such time as the concerned national competent authorities consider that the risk profile of the product has been sufficiently characterised and all appropriate risk mitigation and surveillance measures have been implemented.