Annex I

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for lanthanum, the scientific conclusions are as follows:

Lanthanum deposition

In a literature review performed by the MAH several publications have described cases of lanthanum deposition in the gastrointestinal tract, including biopsy cases confirmed by electron microscopy. In addition, spontaneous cases of lanthanum deposition have been received during the reporting period in association with the use of lanthanum. Although the clinical significance of this finding is yet unknown a causal relationship cannot be excluded. Therefore, considering the data presented during this PSUR, the PRAC considers that the product information of lanthanum containing medicinal products should be amended to reflect the current knowledge on deposition of lanthanum in human tissues.

Gastrointestinal complications

Cases of gastrointestinal obstruction and gastrointestinal perforations associated with the treatment of lanthanum have continued to be observed during the reporting period, occurring mainly in patients at high risk for bowel obstruction. Therefore, the PRAC is of the opinion that a warning should be included in the product information for lanthanum containing medicinal products in order to alert physicians and patients of early signs and symptoms of gastrointestinal disorders, especially constipation and abdominal pain/distension which may indicate bowel obstruction, ileus or subileus.

In addition, serious gastrointestinal complications have been reported in association with unchewed or incompletely chewed lanthanum tablets. Therefore, the PRAC recommends strengthening the wording of the product information on the risk of serious gastrointestinal complications associated with unchewed or incompletely chewed tablets containing lanthanum.

The CMDh agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the Marketing Authorisation(s)

On the basis of the scientific conclusions for lanthanum the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing lanthanum is unchanged subject to the proposed changes to the product information.

The CMDh reaches the position that the marketing authorisation(s) of products in the scope of this single PSUR assessment should be varied. To the extent that additional medicinal products containing lanthanum are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that the concerned Member States and applicant/marketing authorisation holders take due consideration of this CMDh position.

Annex II

Amendments to the product information of the nationally authorised medicinal product(s)

Amendments to be included in the relevant sections of the Product Information (new text **underlined and in bold**, deleted text ~~strike through~~)

Summary of Product Characteristics

For chewable tablets and oral powder

- Section 4.4 Special warnings and precautions for use

A warning should be revised as follows:

Tissue deposition of lanthanum has been shown with Fosrenol in animal studies. In 105 bone biopsies from patients treated with Fosrenol, some for up to 4.5 years, rising levels of lanthanum were noted over time (see section 5.1). ~~No clinical data are available on deposition of lanthanum in other human tissues.~~ **Cases of lanthanum deposition in gastrointestinal mucosa, mainly after long term use, have been reported. The clinical significance of this finding is yet unknown.** The use of Fosrenol in clinical studies beyond 2 years is currently limited. However, treatment of subjects with Fosrenol for up to 6 years has not demonstrated a change in the benefit/risk profile.

A warning should be added as follows:

[…]

There have been cases of gastrointestinal obstruction, ileus, subileus, and gastrointestinal perforation reported in association with lanthanum, some requiring surgery or hospitalization (see section 4.8).

[…]

Exercise caution in all patients predisposed to gastrointestinal obstruction, ileus, subileus and perforation; for example those with altered gastrointestinal anatomy (e.g., diverticular disease, peritonitis, history of gastrointestinal surgery, gastrointestinal cancer and gastrointestinal ulceration), hypomotility disorders (e.g., constipation, diabetic gastroparesis) **and when used with medications known to potentiate these effects.**

During treatment with lanthanum carbonate, physicians and patients should remain alert for signs and symptoms of gastrointestinal disorders, especially constipation and abdominal pain/distension which may indicate bowel obstruction, ileus or subileus.

Treatment with lanthanum carbonate should be re-evaluated in patients who develop severe constipation or other severe gastrointestinal signs and symptoms.

Only for chewable tablets

- Section 4.4 Special warnings and precautions for use

<Product name> tablets must be chewed completely and not swallowed whole ~~to reduce the risk of serious adverse gastrointestinal complications~~(see section 4.2). **Serious gastrointestinal complications have been reported in association with unchewed or incompletely chewed <Product name> tablets.**

Package Leaflet

For chewable tablets and oral powder

- Section 4. Possible side effects:

Some side effects could be serious. If you get any of the following side effects, seek immediate medical attention:

- Rupture in the intestinal wall (signs include: severe stomach pain, chills, fever, nausea, vomiting, or a tender abdomen). This is a rare side effect (may affect up to 1 in 1,000 people).
- Blockage in the intestine (signs include: severe bloating, abdominal pain, swelling or cramps, severe constipation). This is an uncommon side effect (may affect up to 1 in 100 people).
- **Contact your doctor if you experience new or severe constipation, it could be an early sign of a blockage in your intestine. Constipation is a common side effect (may affect 1 in 10 people).**

Other less serious side effects include the following:

Very Common side effects (may affect more than 1 in 10 people):

- Nausea, vomiting, diarrhoea, stomach pain, headache, itching, rash.

Common side effects (may affect up to 1 in 10 people):

- ~~Constipation~~, ~~h~~**H**eartburn, flatulence.
- Hypocalcaemia (too little calcium in your blood) is also a common side effect; the symptoms of which can include tingling in the hands and feet, muscle and abdominal cramps or spasms of the facial and feet muscles.

~~Please inform your doctor if you experience constipation. This can be an early symptom of a blockage in your intestine.~~

Only for chewable tablets

- Section 2. What you need to know before you take lanthanum carbonate:

Warnings and precautions:

[…]

It is very important to chew completely <Product name> tablets and not to swallow them whole or incompletely chewed. This will reduce the risk of adverse gastrointestinal complications like rupture in the intestine wall, blockage in the intestine, constipation (see section 4).

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	December 2017 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	27 January 2018
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	28 March 2018