FINAL ASSESSMENT REPORT
Procedure number AT/H/PSUR/0019/002

Active substance	**Lactitol monohydrate**
Innovator name of product in the P-RMS	**Importal / Emportal / Portolac**
<for MRP products also procedure number>	
Pharmaceutical form(s)/strength	**66.67% oral solution** **100% powder for oral solution**
MAH(s)	**Novartis Consumer Health SA**
HBD and DLP	**HBD: 03 Sep 1985** **DLP Sep 2012**
PSUR period	**01 OCT 2009 – 30 SEP 2012**
P-RMS	**Austria**
Assessor	**Dr. Irmgard Resch**
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TIME TABLE

Procedure Start Date	**27-JAN-2013**
Date of preliminary AR	**28-MAR-2013**
Deadline for comments to P-RMS	**27-APR-2913**
Clockstop/ RFI / LoQ	**08-MAY-2013**
Procedure Restart Date	**08-JUL-2013**
Date of Draft Final AR	**08-JUL-2013**
Deadline for comments to P-RMS	**23-JUL-2013**
Date of Final AR	**24-JUL-2013**
Discussion at PhVWP	
DLP of the next PSUR submission and period of PSUR	**23-SEP-2015**

In addition to the innovator PSUR, the assessment report covers the following PSURs of additional products authorised in the P-RMS:

MAHs	MR procedure number (if applicable)	Period covered by the PSUR
none		

The following PSURs of products <u>not authorised in the P-RMS</u> have been submitted as part of the worksharing procedure.

MAHs	MR procedure number (if applicable)	Period covered by the PSUR

INDICATIONS AUTHORISED IN THE P-RMS (INNOVATOR):

Symptomatic treatment of constipation
Treatment of hepatic encephalopathy

WORLDWIDE MARKETING AUTHORISATION STATUS AND UPDATE OF REGULATORY ACTIONS TAKEN FOR SAFETY REASONS (MAH, AUTHORITIES)

Has there been a change to the marketing authorisation status or have regulatory actions been taken for safety reasons? Yes ☒ No ☐

If yes, specify:

Change of MAH

Importal was first registered in Switzerland by Novartis Consumer Health S.A. (NCH) in 1985 and was subsequently marketed in various European Countries. On April 5th, 2011, ACRAF S.p.A. and NCH entered into an "Asset purchase agreement" according to which duty of care for the product was transferred from NCH to ACRAF in the following countries (Austria, Belgium Cyprus, Greece, France, Germany, Italy, Luxembourg, The Netherlands, Spain, Portugal, Switzerland, Sweden).

From the date of authorization of the drug, no actions have been taken by the Regulatory Authorities or MAH for safety reasons.

SUMMARY OF PREVIOUS RELEVANT PhVWP/CHMP DISCUSSIONS *, IF ANY:

Not applicable

* During the period under review

CHANGES TO REFERENCE SAFETY INFORMATION

Is the CCDS the reference document? Yes ☐ No ☒

If not, please indicate which document is used as reference document:

The reference document is the English translation of the Italian SmPC

The MAH provided 2 SmPCs, one for the indication "Short term treatment for occasional obstipation" and one for "Prevention and treatment of subclinical, acute and chronic porto-systemic encephalopathy: Prophylaxis of hepatic pre-coma and coma. Hepatic cirrhosis"

Date of the last reference document: *November 2011 for both documents*

Which sections of the reference safety document have been changed during the period covered by the PSUR?

☐ posology and method of administration (4.2)
☐ contraindications(4.3)
☒ special warnings and precautions for use(4.4)
☒ interaction with other medicinal products and other forms of interaction(4.5)
☐ pregnancy and lactation (4.6)
☐ effects on ability to drive and use machines(4.7)
☐ undesirable effects(4.8)
☒ overdose (4.9)

Please specify the safety relevant changes:

Separation into two SmPCs, one for "Short term treatment for occasional obstipation" and one for "Prevention and treatment of subclinical, acute and chronic porto-systemic encephalopathy: Prophylaxis of hepatic pre-coma and coma. Hepatic cirrhosis"

Section 4.4.
In the case of intestinal meteorism, the treatment should be started with the minimum doses indicated, gradually increasing according to the effect obtained.
Portolac has no carcinogenic effect.
Keep all medicinal products out of the reach and sight of children.

The abuse of laxatives (frequent or prolonged use or with excessive doses) can cause persistent diarrhoea with consequent loss of water, mineral salts (especially potassium) and other essential nutrients.
In more severe cases, dehydration or hypopotassemia may arise, which can lead to heart or neuromuscular dysfunctions, especially in the case of the simultaneous treatment with cardiac glycosides, diuretics or corticosteroids.
The abuse of laxatives, especially contact laxatives (stimulating laxatives), can cause dependency (and, therefore, the possible need to progressively increase the dosage), chronic constipation and loss of normal intestinal functions (intestinal atony).

The treatment of chronic or recurrent constipation always requires medical attention for a diagnosis, the prescription of medicines and supervision during the therapy.
You must therefore consult a doctor when the need for laxatives derives from a sudden change in previous intestinal habits (frequency and characteristics of the evacuations) lasting more than two weeks or when the use of laxatives no longer produces effects.
It is also advisable that the elderly and those who are not in good health consult a doctor before taking the medicine.

Section 4.5.:
In the case of intestinal dysmicrobism, note that broad-spectrum antibacteria agents and antacids, administered by mouth simultaneously with lactitol, can decrease the effects of the product on the intestinal microflora.

Laxatives can reduce the time spent in the intestine and consequently the absorption of other pharmaceuticals administered by mouth.
Hence, laxatives should not be taken at the same time as other medicines: after taking a medicine, wait at least 2 hours before taking the laxative.

Section 4.9.:
Excessive doses may cause abdominal pain and diarrhoea; consequent losses of liquids and electrolytes must be replaced.

Assessor's comment:
The MAH implemented the changes requested during the last PSUR Work Sharing procedure in the SmPC. Some additional changes have been made by the MAH in sections 4.4., 4.5, 4.9. of the SmPC. Moreover, the two indications have been covered in two separate documents.
However these changes have not been mentioned in chapter 4. Changes in Reference Safety Information of the PSUR.
It is recommended to delete the subheadings "Warnings" and "precautions for use" within section 4.4 of the SmPC as these are covered by the main heading.

Selected differences between RSI and proposed CSP:
Not applicable

SUSPECTED ADVERSE DRUG REACTIONS (INNOVATOR) DURING THE PERIOD

SERIOUS CASES AND ADRs

Total number of serious cases, incl. fatalities	6
Number of fatal cases	1

SUSPECTED ADVERSE DRUG REACTIONS, overview

ADRs	Serious		Non-Serious	
	Listed	Unlisted	Listed	Unlisted
Immune system disorders				
Edema mouth				1
Lip swelling				1
Swollen tongue				2
Systemic inflammatory response syndrome		1		
SUB-TOTAL		*1*		*4*
Gastrointestinal disorders				
Oral pruritus				1
Lip pruritus				1
Pancreatitis acute		1		
Nausea			1	
Abdominal pain			1	
Abdominal pain upper	1		1	
Diarrhoea	1		1	
Dyspepsia				1
Constipation				1
Abdominal distension			3	
Abdominal discomfort			2	
Flatulence			1	
SUBTOTAL	*2*	*1*	*10*	*4*
Psychiatric disorders				
Confusional state		1		
Disorientation		1		
Intentional drug misuse		1		2
SUB-TOTAL		*3*		*2*
Hepatobiliary disorders				
Hepatitis fulminant		1		
SUBTOTAL		*1*		

ADRs	Serious		Non-Serious	
	Listed	Unlisted	Listed	Unlisted
Nervous system disorders				
Epilepsy		1		
SUB-TOTAL		*1*		
Injury, poisoning and procedural complications				
Overdose		2		3
Incorrect drug administration duration				1
SUB-TOTAL		*2*		*4*
General disorders and administration site conditions				
Death		1		
Oedema peripheral		1		
Malaise		1		
Condition aggravated				1
Concomitant disease aggravated		1		
Drug ineffective				5
Therapeutic response decreased				2
No adverse reaction			1	
SUBTOTAL		*4*	*1*	*8*
Renal and urinary disorders				
Renal failure		1		
SUB-TOTAL		*1*		
Metabolism and nutrition disorders				
Dehydration		1		
Hyperglycaemia		1		
Abnormal weight gain		1		
Hyponatraemia		1		
SUB-TOTAL		*4*		
Skin and subcutaneous tissue disorders				
Pruritus				1
SUB-TOTAL				*1*
Investigations				
Blood pressure decreased		1		
Blood potassium decreased		1		
SUB-TOTAL		*2*		
TOTAL	*2*	*20*	*11*	*23*
GRAND TOTAL	**56**			

CASE BREAKDOWN

	UNEXPECTED	EXPECTED	Total
SERIOUS	6	0	6
NON SERIOUS	8	6	14
TOTAL	**14**	**6**	**20**

TABLE OF SELECTED* SERIOUS UNLISTED ADRs :

Serious unlisted ADRs (MedDRA PT in agreed SOC order)	Number of serious unlisted ADRs
See section "Overall assessor comments on case reports" of this assessment report	

* Selection is within the discretion of the P-RMS

VALUABLE INFORMATION FROM PSURs FOR OTHER PRODUCTS AUTHORISED IN THE P-RMS

Do any of the PSURs for other products authorised in the P-RMS contain information not addressed in the PSUR for the originator product(s)?

Yes ☐ No ☒

If yes, specify in table below:

TABLE OF SELECTED* SERIOUS UNLISTED ADRs IN OTHER PSURs AUTHORISED IN THE P-RMS

Serious unlisted ADRs (MedDRA PT in agreed SOC order)	Number of serious unlisted ADRs

* Selection is within the discretion of the P-RMS

Other information:

OVERALL ASSESSOR COMMENTS ON CASE REPORTS (INCL. LITERATURE CASES)

Describe and comment on ADRs of importance from individual case histories.

Fatal cases:

10018065 - General disorders and administration site conditions
NOV-RA-2012-0015- FRANCE
DEATH - MALAISE- DEHYDRATION- RENAL FAILURE- BLOOD PRESSURE DECREASED- SYSTEMIC INFLAMMATORY RESPONSE SYNDROME- OEDEMA PERIPHERAL- HYPERGLYCAEMIA
Case from Novartis (CHPA2012FR000962).

A 94-year-old male was taking Importal and Normacol (sterculia), which he started on unknown dates for constipation. He experienced Malaise, Dehydration, Renal Failure, Blood Pressure Decreased, Systemic Inflammatory Response Syndrome, Oedema Peripheral, Hyperglycaemia and was hospitalized. Importal and Normacol were discontinued. On 21/12/2011 he died. The Health Authority did not consider that the patient's death was related to the side effect of dehydration.

ACRAF's Medical Assessment

ADR(s) characteristics: Seriousness: SERIOUS (PATIENT DIED/INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION); Expectedness: UNEXPECTED; Relationship: UNASSESSABLE

Assessor's comment:
This case lacks details about patient history and concomitant medication.

Other serious cases:

10029205 - Nervous system disorders
NOV-RA-2012-0012 NETHERLANDS – **EPILEPSY; OVERDOSE**
Case from Novartis (CHPA2010NL19102).

A 4-year-old boy with a history of epilepsy, who had been free of seizures for 3 years, experienced an epileptic seizure 36 hours after taking Importal (667mg lactitol, 5mL twice a day for two days) for constipation.
Other event: overdose. The drug was withdrawn and the patient recovered. This is a serious case (medically significant). The event epilepsy was assessed as unlabeled according to the product information. The available information was considered inadequate to fully assess the case.

ACRAF's Medical Assessment
ADR(s) characteristics: Seriousness: SERIOUS (OTHER MEDICALLY IMPORTANT CONDITION); Expectedness: UNEXPECTED; Relationship: POSSIBLE

Assessor's comment:
A possible temporal relationship cannot be excluded.The MAH should provide information about cumulative data regarding epilepsy and seizures, try to get additional information about this case and clarify, why this is considered an overdose.

10037175 - Psychiatric disorders
NOV-RA-2012-0014 ITALY - **DISORIENTATION- HYPONATRAEMIA - CONFUSIONAL STATE - BLOOD POTASSIUM DECREASED – INTENTIONAL DRUG MISUSE - CONCOMITANT DISEASE AGGRAVATED – DIARRHOEA - OVERDOSE**
Case from Novartis (CHPA2011IT07617).

Initial report received via the Italian Health Authority (IT-MINSAL02-142089). After taking Portolac, Tavor and Tachidol, a 78- year-old woman experienced confusion, disorientation, diarrhoea and hyponatraemia caused by drug abuse. The suspect drugs were withdrawn, she was rehydrated and her condition improved. The causality relationship was assessed as "probable" based on the Naranjo Algorithm used by Centro Regionale Lombardia. All events, except diarrhea, were assessed as unlabelled.

ACRAF's Medical Assessment
ADR(s) characteristics:
Seriousness: SERIOUS (INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION); Expectedness: UNEXPECTED (except Diarrhoea); Relationship: PROBABLE

Assessor's comment:
The causal relationship in this case cannot be excluded, however the assessment is confounded by concomitant drugs (for events confusion, disorientation) and drug abuse of Lactitol (for events diarrhoea, hyponatraemia).

10017947 - Gastrointestinal disorders
NOV-RA-2012-0011 - FRANCE – **PANCREATITIS ACUTE - ABDOMINAL PAIN UPPER**
Case from Novartis (CHPA2010FR01848).

A 42 yr-old male was hospitalized for a pancreatitis episode. He was taking IMPORTAL; ABILIFY; MEPRONIZINE MEDIATOR; IXPRIM; EUPANTOL ; OMIX; AVLOCARDYL; LAROXYL; TRANXENE; IMOVANE. Concomitant drug: MYCOSTER.

ACRAF Medical Assessment
ADR(s) characteristics:Seriousness: SERIOUS (INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION); Expectedness: UNEXPECTED (PANCREATITIS ACUTE), EXPECTED (ABDOMINAL PAIN UPPER);Relationship: POSSIBLE

Assessor's comment:
This serious unlisted case concerns an isolated case in the current PSUR period with several concomitant drugs as a confounding factor. No further action is necessary.

10019805 - Hepatobiliary disorders
NOV-RA-2012-0013 FRANCE **HEPATITIS FULMINANT**
Case from Novartis (CHNY2011FR000482).
A 53-year-old female patient who was treated with IMPORTAL for constipation, LAROXYL, ATHYMIL and TERCIAN for depression and with BIPROFENID for arthritic pain, was hospitalized for fulminant hepatitis. Orthotopic liver transplantation was performed. The health Authority assessed the relationship between IMPORTAL and the AE as unlikely. Novartis.
Comm:serious and unlisted ADR, however other alternative causes (other drugs) provide a possible explanation for the ADR.

ACRAF's Medical Assessment
ADR(s) characteristics:.
Seriousness: SERIOUS (INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION/ LIFE THREATENING); Expectedness: UNEXPECTED;
Relationship: UNLIKELY

Assessor's comment:
Assessor agrees that a causal relationship between fulminant hepatitis and lactitol treatment is unlikely and that the concomitant medication provides a possible explanation.

10027433 - Metabolism and nutrition disorders
LEP-RA-2012-0009 SPAIN
ABNORMAL WEIGHT GAIN Case from AngeliniSpain(ANG-ES12-074).
A 55-year old male patient, included in study "Influence of certain genetic polymorphisms in obesity induced by antipsychotics", was on Emportal 10g for constipation, risperidone 6ml for paranoid schizophrenia, diazepam 10g for insomnia, AKINETON 4mg.
Concomitant Drug:RISPERDAL 50mg. He experienced an abnormal weight increase (7.2kg in 6 months) Outcome: not recovered. Medical Assessment: the SPC of EMPORTAL does not mention abnormal weight increase as a possible adr for this drug.

ACRAF's Medical Assessment
ADR(s) characteristics: Seriousness: SERIOUS (OTHER MEDICALLY IMPORTANT CONDITION) Expectedness: UNEXPECTED Relationship: POSSIBLE

Assessor's comment:
As this case is confounded by concomitant medication and patient history, the causal relationship cannot be assessed.

OVERALL ASSESSOR COMMENTS ON MAH SPONSORED STUDIES

Describe and comment on studies of relevance to safety of the product(s)

During the period covered by this report, no clinical trials sponsored by ACRAF S.p.A. were conducted with

Lactitol.

OVERALL ASSESSOR COMMENTS ON STUDIES FROM THE LITERATURE

Describe and comment on literature studies of relevance to safety of the product(s).

Some clinical studies involving the product Lactitol appeared in international literature.

Assessor's comment:
No new safety issues have been identified in the above mentioned studies.

OVERALL ASSESSOR COMMENTS ON NEW INFORMATION REGARDING

Special populations:

Two elderly patients and a 4-year-old child experienced adverse events associated with the use of EMPORTAL/IMPORTAL/PORTOLAC.

- A 94-year-old male who had taken Importal for constipation was hospitalized and died. The Health Authority did not consider that the patient's death was in relation to the adverse drug event of dehydration.
- A 78-year-old female experienced confusion, disorientation, diarrhoea and hyponatraemia caused by drug abuse. The patient improved after suspect drug withdrawal and reydration.
- A 4-year-old boy with a history of epilepsy experienced an epileptic seizure after an overdose.

These cases do not represent an emerging signal of risk for special population groups.

Assessor's comment:
Two cases occurred in the elderly and one case in the paediatric population during the PSUR period.
No emerging signal of risk can be currently identified, neither in the paediatric nor in the elderly population.

Pregnancy/lactation:
No new information available

Drug interaction:
no new information available

Overdose:
No information provided by MAH

Abuse or misuse:
There were 9 ADRs pertaining to abuse/incorrect use of the drug (5 overdose, 3 intentional drug misuse, 1 Incorrect drug administration duration) occurring in 6 patients. One of these patients experienced no adverse reactions. Two of the 6 cases were serious. Of the two serious cases, one involved a 4-year-old male with a history of epilepsy, who experienced an epileptic seizure after taking an overdose of Importal for constipation. The drug was withdrawn and the patient recovered. The other serious case concerned a 78-year-old female who experienced confusion, disorientation, diarrhoea and hyponatraemia caused by drug abuse. The patient improved after suspect drug withdrawal and reydration.
These cases do not represent an emerging signal.

Assessor's comment:
The warning to abuse lactitol is covered by the SmPC. No new safety signal arises from the abuse and misuse cases from the current period.

Medication errors:
No information provided by MAH

Long-term treatment:
No information provided by MAH

Off label use:
No information provided by MAH

Late-Breaking Information

On November 15th 2012, the following case, occurring in Sweden, was received by ACRAF's HQ Pharmacavigilance Department:
Following surgery, a 50-year-old female used Imporal 1 dose (oral powder) in the evening as prescribed by her physician. She very soon experienced bloated abdomen, abdominal pain, diarrhea and wind. The case will be discussed in the next planned PSUR for the product.

COMMENTS ON ANY CHANGE OF THE RISK BENEFIT BALANCE

MAH conclusion:

The analysis of the ICSRs collected during the reporting period has shown that the most frequently involved system-Organ Class (SOC) was the Gastrointestinal disorders SOC.
This is not surprising since the indication of Portolac/Lactitol/Emportal, as well as most of the undesirable effects listed in the reference information (SPC), fall within this SOC. Indeed, almost all of the ADRs falling under this SOC were expected.
The General disorders and administration site conditions was the next most represented SOC, in which almost half of the ADRs involved drug inefficacy or decreased efficacy and 1 ADR was a "no adverse reaction" registered to indicate that no adverse effect was experienced in a case of overdose.
Next most represented were the Immune system disorders SOC, which however comprised ADRs all pertaining to the same systemic allergic reaction experienced by a single patient, and the Injury, poisoning and procedural complications SOC, consisting entirely of cases of incorrect product administration (overdose and incorrect drug administration duration).
Of the six serious cases (all unexpected), one involved the death of an elderly patient.
The Health Authority did not consider his death to be related to the side effect of dehydration.
There were also three cases of pancreatitis, fulminant hepatitis and abnormal weight gain.
The two remaining serious cases involved incorrect product use: in one case a 4-year old boy with a history of epilepsy experienced an epileptic seizure after an overdose. In the other, an elderly woman experienced various ADRs after intentional drug misuse and overdose.

The most frequently observed adverse reactions were reactions pertaining to incorrect product use (9 ADRs), 5 cases cases of drug inefficacy and 3 cases of abdominal distension, which is among the listed undesirable effects for Emportal/Imporal/Portolac.

In light of these conclusions, no emerging signals that could have an impact on the risk/benefit profile of the product PORTOLAC/IMPORTAL/EMPORTAL have been detected.

According to the PORTOLAC / EMPORTAL / IMPORTAL Summary of Product Characteristics (SmPC) in each country where it is authorized as an OTC drug, the indication for self-medication is the symptomatic treatment of constipation.
Indications as a prescription drug also include the treatment of Hepatic Encephalopathy (HE).

The efficacy of the drug in the above reported indications is confirmed by some articles published in scientific literature.

Lactitol and constipation

Three papers (two reviews and one clinical trial) confirming the efficacy of lactitol are reported below.

- ☐ In an open trial, the efficacy and safety were demonstrated in 114 chronically constipated patients of both sexes, aged 18-70, without any organic alteration of the colon (Delas 1991). Clinical efficacy was reached in 80% of patients with a dosage of 20 g, as single dose in the evening. All patients, except one, agreed with the packaging and the taste of the product.
- ☐ A recent review on the use of lactitol in constipation (Faruqui, 2012), reported that it offers superior efficacy compared to lactulose, better tolerability and palatability. In addition, the cathartic effect of lactitol is more predictable. According to the authors' opinion, lactitol appears to be the ideal successor to lactulose for the treatment of constipation.
- ☐ A systematic review on the use of lactitol and lactulose in the treatment of chronic constipation, published in 2010 on the *J Indian Med Assoc*., showed that lactitol should be preferred over lactulose in the management of chronic constipation because of its superior efficacy as judged by physicians, better palatability, lesser incidence of adverse events, better acceptance and compliance reported by patients.

Lactitol and Hepatic encephalopathy (HE)

HE is a reversible neuropsychiatric syndrome associated with chronic and acute liver dysfunction, showing significant morbidity and mortality. The efficacy of lactitol in the treatment of HE, alone or in combination with other drugs, was confirmed in the following articles.

- ☐ One paper (Foster 2010), focused on the current and emerging strategies for treating HE, including the use of non-absorbable disaccharides (lactulose and lactitol) in the pharmacologic therapy of the disease.
- ☐ A recent meta-analysis of randomized trials (Gluud 2012), showed that non-absorbable disaccharides have beneficial effects on HE manifestations and in the prevention of HE episodes, when compared with placebo or no intervention. The addition of rifaximin to nonabsorbable disaccharides showed an additional benefit.
- ☐ Current trends in the treatment of HE indicate lactulose and lactitol as first-line treatment (Al Sibae 2009). In fact, clinical trials have established their efficacy when used as enemas, and extensive clinical experience with oral administrations demonstrated their efficacy in producing two to three soft bowel movements a day for the treatment of chronic HE. For patients unable to tolerate lactulose or lactitol or who have persistent chronic HE with lactulose or lactitol, second-line agents such as neomycin, metronidazole and rifaximin are employed.

In conclusion, the wide clinical use of the drug in both indications, and recent literature data confirm that lactitol's efficacy profile fully balances any potential related risk.

Assessors overall conclusion on benefit risk balance

It can be concluded that the benefit risk ratio of Lactitol remains unchanged.

ACTION PLAN AND CONCLUSIONS

A CHANGES OF THE BENEFIT RISK BALANCE

Has the benefit risk balance changed?

No ☒

Yes ☐ , please specify:

B CHANGES REQUIRED IN THE CSP

Is the CSP acceptable?

Yes ☐ No ☐ not applicable

If not, specify the necessary changes (specific wordings):

Based on the new legislation the updates of the CSP are no longer required in the frame of PSUR Work-sharing procedure.

The RSI, which has been provided by the MAH, is the English version of the Italian SmPCs (for two different indications: obstipation and porto-systemic encephalopathy / hepatic cirrhosis).

These EU-SmPCs are considered acceptable and should be the basis for variations in the MSs, where applicable. The MAH should however clarify discrepancies of the frequency of unusual gastrointestinal rumbling /sounds. They are classified as: unknown, occasionally and/or rare in the national SmPCs.

The MAH should estimate the frequency of these PTs in accordance with the post-marketing cumulative experience and the data from studies (if available). The rationale for the frequency category for ADRs should be explained in a sub-section of the SmPC.

The 3/X frequency calculation formula as mentioned in the Guideline on Summary of Product Characteristics (SmPC), September 2009, should be used for adverse reactions from spontaneous reporting when adverse reaction has never been observed in clinical trials.

C REGULATORY ACTIONS * PROPOSED, IF ANY

An update of the product information is expected within 4 months of receiving the final assessment report.

* Regulatory options may include urgent safety restrictions, variations, suspension or revocation. Topics for close monitoring should be mentioned below in section E.

D SUMMARY OF COMMENTS FROM OTHER MSs

Member State	Comment	Agreed action e.g. updating CSP, close monitoring
No comments received		

E POINTS TO BE ADDRESSED IN THE NEXT PSUR

There are no other issues under close monitoring at the moment.

The data lock point for the next PSUR is 23-SEP-2015, according to the EURD list as published on the EMA website.(28/03/2013).

F RFI / LoQ: REQUEST FOR FURTHER INFORMATION / LIST OF QUESTIONS

Questions to be addressed by the MAH:

1. *The MAH should clarify the frequency of unusual/abnormal gastrointestinal rumbling /sounds. The frequency of these PTs should be estimated based on the post-marketing cumulative experience and the data available from studies. The rationale for the frequency category for ADRs should be explained in a sub-section of the SmPC. The 3/X rule should be used for adverse reactions from spontaneous reporting when adverse reaction has never been observed in clinical trials. (see "A Guideline on Summary of Product Characteristics (SmPC)", September 2009.*

MAH response:

As reported in the Dutch, Swedish, Austrian, Cypriot, Spanish an Swiss SmPCs the sources of adverse drug reactions were clinical trials and post-marketing experience (please refer to Appendix n. 1 of the PSUR).

Unusual/abnormal gastrointestinal rumbling /sounds have been observed in clinical trials with a frequency assessed as "occasional", while the unknown frequency was referred to post-marketing cases.

The Guideline on Summary of Product Characteristics of September 2009 clearly states that in case of unexpected adverse reaction detected from spontaneous reporting, each adequately designed study where this adverse reaction could have been detected should be reviewed to choose a frequency category. However, this is not applicable to our case because the discussed ADR is not unexpected and already reported in the SmPC with a specific frequency.

In addition, for the adverse reaction that has never been observed in clinical trials the Guidance asks to apply the 3/X rule. But, once again, this is not the case for unusual/abnormal gastrointestinal rumbling /sounds.

A part from adverse drug reactions occurring at the start of treatment (i.e., abdominal discomfort, flatulence, abdominal pain, abdominal distension), other adverse drug reactions already reported in the SmPC as observed in clinical trials, were also listed as spontaneous reports (i.e., vomiting, diarrhea, anal itching, nausea). This is not fully compliant with the specific Guidance.

To avoid confounding situations, the MAH proposal is to apply the requirements of the Guideline on Summary of Product Characteristics. In particular, the MAH suggests to delete from section 4.8 of the SmPC the adverse reactions referred to the post-marketing experience since they were already observed in clinical trials, and to modify Section 4.8 as following (changes are in *italic* and <u>*underlined*</u>).

Frequencies were extrapolated from the wording reported in the approved SmPC, giving priority to data from clinical trials, and upgrading frequencies from spontaneous reports in some cases. The MedDRA classification was also applied.

4.8. Undesirable effects

At the start of treatment, Portolac may produce abdominal discomfort, especially flatulence and, albeit rarely, abdominal pain or, at times, abdominal distension. Such discomfort disappears or improves after a few days of regular treatment with Portolac.

~~*<u>Occasionally, nausea, rumbling and anal itching have been observed, as well as rare cases of vomiting.</u>*~~ Due to inter-individual differences, some patients, even when taking the recommended does, may experience diarrhea. Reducing the dose will solve this problem.

The adverse reactions ~~are~~ listed below *were observed in clinical trials and confirmed by the spontaneous reporting.* ~~*with*~~ The *MedDRA* classification for system~~*/and*~~ organ~~*s*~~ ~~*and*~~ *with the following* frequenc*ies* *were used.* ~~*Frequencies are defined as*~~: very common (≥ 1/10), common (~~*from*~~ ≥1/100 to < 1/10), uncommon (~~*from*~~ ≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 *to* < 1/1,000) or very rare (<1/10,000).

SOC / Frequency	***Adverse drug reactions***
Gastrointestinal disorders	
Rare	*abdominal pain, abdominal distension, diarrhea, flatulence, vomiting*
Very rare	*nausea, gastrointestinal sounds abnormal, anal pruritus*

~~*Gastrointestinal disorders:*~~

~~*Very rare: vomiting, abdominal pain, abdominal discomfort, abdominal distension, diarrhea, anal itching, nausea, flatulence.*~~

~~*Unknown: unusual gastrointestinal rumbling*~~

For the sake of clarity, the proposed text for Section 4.8, without tracked changes, is hereinafter reported.

4.8. Undesirable effects

At the start of treatment, Portolac may produce abdominal discomfort, especially flatulence and, albeit rarely, abdominal pain or, at times, abdominal distension. Such discomfort disappears or improves after a few days of regular treatment with Portolac.

Due to inter-individual differences, some patients, even when taking the recommended does, may experience diarrhea. Reducing the dose will solve this problem.

The adverse reactions listed below were observed in clinical trials and confirmed by the spontaneous reporting. The MedDRA classification for system/organ with the following frequencies were used: very common (≥ 1/10), common (≥1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) or very rare (<1/10,000).

SOC / *Frequency*	**Adverse drug reactions**
Gastrointestinal disorders	
Rare	abdominal pain, abdominal distension, diarrhea, flatulence, vomiting
Very rare	nausea, gastrointestinal sounds abnormal, anal pruritus

P-RMS comment:
The changes proposed by MAH are adequate and should be implemented in the respective national product information.
Issue resolved.

2. *MAH should provide information about cumulative data regarding epilepsy and seizures, try to get additional information about case NOV-RA-2012-0012 NETHERLANDS – Epilepsy; Overdose and clarify, why this is considered an overdose case.*

MAH response:

Additional information has been requested and received from Novartis (the previous MAH) on 23/05/2013.

The case, received by Novartis in December 2010 (original code: CHPA2010NL19102) and occurring in the Netherlands, concerns a 4-year-old child with a history of epilepsy who had been free of seizures for 3 years. After taking Importal 667mg/mL for constipation for two days (5 mL twice a day on the first day, followed by a third 5 mL administration on the second day, 36 hours later) the patient experienced an epileptic seizure. The drug was withdrawn and the patient recovered. This report was assessed as a serious (medically significant) unlabeled case of overdose.

The maximum approved daily dose of lactitol syrup in children varies across SmPCs of different member states, as reported in the following table.

Country	Posology of syrup in children
Italy	from 2 to 6 years, 10 ml per day over 6 years, 10-15 ml per day
Netherlands	Children 1 – 6 years: 2.5-7.5 ml Children 6 - 12 years: 7.5-15 ml
Switzerland	Children 1 – 6 years: 3.75-7.5 ml Children 6 – 12 years: 7.5-15 ml

The Dutch case was therefore considered as an overdose since 10 ml per day were administered in a 4-year-old child.

However, the Italian SmPC (the Reference Safety Information for this procedure) indicates 10 ml as the maximum daily dose in the age range 2-6 years. On this basis, the MAH agrees with the Assessor that the report should not be considered as a case of overdose.

A search of MAH's global safety database has retrieved no other epilepsy cases associated with lactitol, but one case of "seizure" in a newborn received from Novartis.

In this patient, forceps were used due to foetal non–progression. The newborn presented convulsions localized to the right half of the body on day 1 with early jaundice. The newborn presented a bilateral parietal cephalhematoma. Transfontanellar ultrasound and CT-scan showed multiple bilateral hemorrhagic foci with extensive oedema. The evolution was favorable after 48 hours with an anti-epilectic treatment. During pregnancy, the mother was treated with several drugs* including lactitol. Considering the forceps-assisted delivery and the concomitant treatment with various drugs during pregnancy, the MAH agrees with Novartis's assessment that alternative causes may provide a possible explanation for the reported adverse event.

In conclusion, the MAH considers case NOV-RA-2012-0012 to be an isolated occurrence and does not consider epilepsy/seizures to be a signal associated with the use of lactitol.

Notes

(*) Parapsyllium (paraffin, liquid, plantago afra, psyllium) and at the beginning of the pregnancy she was treated with Motilium (domperidone), Primperan (metoclopramide) and Vogalene (metopimazine). She also took Furadantine (nitrofurantoin) from 21/101994 for a urinary tract infection. She was treated with Oroken (cefixime) from 14 to 26/11/1194. Following treatment with Oroken she developed pseudomembranous colitis which was treated with oral Vancomycine, She also received Ultralevure (saccharomyces boulardii) for 10 days until 17/12/1994 and Diffu-k (potassium chloride).

P-RMS comment:
It can be agreed that the concomitant medication of the mother during pregnancy is a possible explanation, the case can be considered to be an isolated case.
Issue resolved.

FINAL CONCLUSION (SUMMARY OF A-F)

The benefit risk balance of lactitol remains unchanged.

The changes proposed to section 4.8. of the SmPC regarding gastrointesinal disorders are acceptable.
An update of the product information is expected within 4 months of receiving the final assessment report.

The next PSUR should be submitted in accordance with the requirements of the EURD-list (03-JUL-2013) i.e. the next DLP 23-SEP-2015.

DATE AND CONCLUSION OF PHVWP DISCUSSION CONCERNING THIS PSUR, IF ANY:

Annex I : CSP

The update of the CSP is no longer considered required in the frame of PSUR Work-sharing procedure.

Annex II:

PATIENT EXPOSURE (one annex for each PSUR of products authorised in the P-RMS)

Patient exposure in this PSUR :

The DDD for Lactitol is 10 g.

LACTITOL POWDER 2.5g sachets:
Units sold * 2,5 / 10= patient/day
4,189,110* 2,5 / 10 =1,047,277 patient/day

LACTITOL POWDER (5g sachets):
Units sold * 5 / 10= patient/day
7,749,510* 5 / 10= 3,874,755 patient/day

LACTITOL POWDER 10g sachets
Units sold * 10 / 10= patient/day
243,044,820* 10 / 10= 243,044,820 patient/day

LACTITOL POWDER-200g bottles
Units sold * 200 / 10= patient/day
281,771* 200 / 10= 5,635,420 patient/day

LACTITOL SOLUTION/SYRUP (66.67%)- 200 ml
Units sold * 133,34 / 10= patient/day
2,095,528* 133,34 / 10= 27,941,770 patient/day

LACTITOL SOLUTION/ SYRUP (66.67%)- 500 mL
Units sold * 333,35 / 10= patient/day
1,155,918 * 333,35 / 10= 38,532,526 patient/day

TOTAL PATIENT/DAY ADMINISTRATIONS
The total estimated number of patient/day administrations for Portolac/Emportal/Importal is therefore 320,076,568.
Considering a mean therapeutic cycle of 3 days and a mean number of 3 treatments per year per patient (9 treatments per patient in the period considered):

LACTITOL POWDER 2.5g sachets:
1,047,277 / 3 / 9 = 38,788 patients treated

LACTITOL POWDER (5g sachets):
3,874,755 / 3 / 9 = 143,509 patients treated

LACTITOL POWDER 10g sachets
243,044,820 / 3 / 9 = 9,001,660 patients treated

LACTITOL POWDER-200g bottles
5,635,420 / 3 / 9= 208,719 patients treated

LACTITOL SOLUTION/SYRUP (66.67%)- 200 ml
27,941,770 / 3 / 9 = 1,034,880 patients treated

LACTITOL SOLUTION/ SYRUP (66.67%)- 500 mL
38,532,526 / 3 / 9= 1,427,131 patients treated

TOTAL PATIENT EXPOSURE
The total estimated number of patients treated with Portolac/Emportal/Importal is therefore 11,854,687.

Methodology used for the exposure number calculation :

☐ Defined Daily Dose
☒ patients/day
☐ number of prescriptions
☐ number of doses
☒ Other (please specify) patients treated

Comparison with previous PSUR, if information is available

Change in methodology used for calculation:
Yes ☐ No ☒

Overall change in patient exposure:
Yes ☒ No ☐

Increase ☐ Decrease ☒

Annex III: COMMENTS ON THE PSUR (annex exclusively for innovator MAH)

Is the PSUR in accordance with international guidelines (CIOMS II, Volume 9A) ?

Yes ☒ No ☐

If not, specify non-conformance with the guidelines