15 March 2024
EMA/CHMP/426533/2019
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Information for the package leaflet regarding proline used as an excipient in medicinal products for human use' (EMA/CHMP/332530/2015)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	CSL Behring AG
2	Medicines for Europe
3	F. Hoffmann–La Roche Ltd
4	EFPIA

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	The highest dose of Privigen approved in the EU region is 2 g/kg (Kawasaki disease), corresponding to 0.58 g of proline per kg. No cases of proline-related toxicity have been identified from the monthly review of Privigen data over 11 years in the market. A dose of proline of 0.58 g/kg can therefore be considered as safe. The highest tolerable proline dose in humans is not known. Kawasaki disease occurs typically in children, therefore this dose can also be considered as safe in children. CSL Behring recommends that the guideline should compare the animal doses to the highest single dose of proline that has been found to be safe in humans.	
	CSL Behring would like to point out that the causal link between hyperprolinemia and neurological symptoms is plausible, but unproven (these symptoms could be due e.g. to other effects of the enzyme's defects).	Agreed, there is a likely but no causal association.
	There should be adequate description of all excipients such as proline and glycine for balanced guidance of health care professionals and patients. Glycine is widely used as excipient for IgG products although there are defects in glycine metabolism. See also comment on line 158. Would the EMA agree to issue guidelines on all stabilizers used in IVIG SCIG and IMIG, including glycine, at the same time? This would avoid misinterpretation that stabilizers for which guidelines are not (yet) available are safer than those with specific guidelines.	At the time of publishing this document, there is currently no plans to issue further guidance neither on glycine nor on other stabilizers.

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	In general the draft guideline is in need of language improvement. There are instances of repeated sentences on the same page, incomplete sentences, typos, errors in reporting data and numbers. The abbreviation for liter (L or l) should be harmonized.	Agreed and changed.
2	The Annex provides a mandatory wording only for the PIL, but no wording is given for the SmPC. The problem is that all MAHs decide on their own about the wording in the SmPC which gives avoidable room for discussion with authorities. The consequence will be that texts are not harmonized in this respect. This aspect was also discussed in the CMDh meeting with representatives of Interested Parties (Minutes for the meeting on 29 May 2018): "Question 7: Implementation of Annex to the EC guideline An update of the SmPC will be needed, but the guideline is specific to the PL and labeling and will therefore not contain wording for the SmPC. The expressed need to have a common wording for the SmPC will be also shared with the EMA for further consideration." -> Therefore we suggest to add a common wording for the SmPC.	Guidance on the SmPC is not within the scope of the revision of the guideline on excipients labelling. It is up to the MAH to define the appropriate wording in the SmPC based on their data.
3	Information included in the Package Leaflet is required to be derived from SmPC (Article 59(3) of Directive 2001/83/EC), particularly those information relating to safe and effective use of the medicinal product. We have noticed that the required new additions in PL for the purpose of mitigating the risks associated with these excipients have not been requested to be reflected in SmPC. In addition, providing the corresponding information also in SmPC will help HCPs to better understand the risk and to advise patients appropriately.	See above Guidance is provided in the QRD-document https://www.ema.europa.eu/en/documents/template-form/qrd-product-information-annotated-template-english-version-103_en.pdf
4	It would be helpful to have further guidance on the location in the package leaflet (PL) for the required text.	The GL on *Excipients in the labelling and package leaflet*

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	• Currently it is up to the MAH to decide, and then in turn at the assessor's discretion. This may lead to inconsistency in the PL between MAH of products with the same excipient. In the case of the proposed statements for proline, would the first paragraph reside in section 6 of the PL and the second and third reside in section 2, or would all paragraphs reside in section 2?	*of medicinal products for human use* indicates the information that should be presented in the package leaflet. In principle this should be reflected in one section of the PL, however, it may also be presented in multiple sections. Further guidance is provided in the QRD-document (see above).
4	It is proposed that to minimize the risk in patient with hyperprolinaemia, a warning/precaution should be also included in SmPC.	See above

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
51-52	1	**Comments:** Red = new suggested or corrected text. **Proposed change:** "In patients suffering from hyperprolinaemia Type I and II, two rare autosomal recessive inherited disorders leading to a dysfunction of proline metabolism resulting in elevated plasma proline levels (normal…"	Accepted.
54-55	1	**Comments:** These lines seem to indicate that proline is be connected to neurological abnormalities. A slight text change is proposed to indicate that despite the absence of evidence exposure of HP I and II patients should be minimized. This should be addressed consistently throughout the document. The genetic defects may cause these neurological abnormalities through other mechanisms. Red = new suggested or corrected text **Proposed change:** "~~Consequently~~ Despite the absence of evidence that these neurological manifestations are caused by proline, additional exposure of these patients to proline should be limited…"	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
62 Table, Row 1 All routes, threshold Zero	3	**Comments:** To minimize the risk in patient with hyperprolinaemia, a warning/precaution should be also included in SmPC **Proposed change:** Propose change to comments column: *Use in patients suffering from hyperprolinaemia only if strictly necessary (e.g. if no alternative treatment is available).* ***A warning/precaution for avoiding using the product in patients suffering from hyperprolinaemia should be included in SmPC.***	Not accepted. The SmPC and the PIL should be in line with each other, but specific guidance on the SmPC is not within the scope of the revision of the guideline on excipients labelling.
62 (executive summary) New information to be included in PIL	4	**Comments:** The majority of companies has no comments. However, one company remarked that in essence, in patients suffering from hyperprolinaemia, exposure to proline should be minimised. Therefore it is suggested to consider to restrict the use in patients suffering from hyperprolinaemia to situation in which it is strictly necessary (e.g. if no alternative treatment is available). This wording should then be reflected in PIL and SMPC.	See above
97-99	1	**Comments:** Concerning oral nutritional supplements, please note that according to the FreAmine package insert, the maximum dose could be up to 168 mg proline/kg/d for adults and 336 mg proline/kg/d for infants. The draft guideline gives a range of 500 mg/d to 1000 mg/d which is not correct.	Reference to the quantity has been removed because it is not relevant to this document (out of scope).

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115-119	1	**Comments:** This paragraph says that the non-clinical studies supporting the approval of Hizentra and Privigen should have been performed in line with GLP guidance … . Actually, many of the supporting studies sponsored by CSL Behring were indeed conducted under GLP requirements as is clearly stated in the study reports and MAA submitted for licensing. CSL Behring suggests to correct this sentence and to note in the following discussion which studies were under GLP. These are noted below.	Accepted.
132	1	**Comments:** Please correct: According to Moreira et al 1989 [23]: Applied daily dose was 12.8 to 18.2 umol/g given twice a day. **Proposed change:** "~~12800~~ 12.8 to ~~16400~~ 18.2 umol of Pro/g bw"	Accepted.
133	1	**Proposed change:** "…plasma proline levels between 1000 and 2000 uM (ten times over normal proline serum levels), similar to those found in hyperprolinemic type II patients…"	Accepted.
150	1	**Comments:** Study 1657/ZLB/02 was conducted under GLP.	Accepted.
158	1	**Proposed change:** "It was concluded that, in contrast to glycine, proline did not …"	Not accepted.

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159	1	**Comments:** Please conclude this sentence with a phrase from line 180 below with the correction of 2.5 instead of 5 times. This is in consideration of the dose for Kawasaki disease: **Proposed change:** "i.e. at doses up to 2.5 times the maximum dose administered with Privigen in humans except for a slight rise of body temperature after 5 days of treatment."	Not accepted, but reference to clinical dose has been removed.
161	1	**Proposed change:** Replace "2-5" with "5".	Accepted.
162	1	**Proposed change:** Replace "once every 2-4 weeks" with "once per week for 3 weeks".	Not accepted. Wording consistent with the EPAR.
166	1	**Comments:** This sentence needs to be rewritten.	Accepted.
177	1	**Comments:** This sentence seems to belong to the previous paragraph.	Accepted.
179-180	1	**Comments:** This sentence could be deleted and part included above in modified form above in line 159. **Proposed change:** ~~No significant 179 effects on behaviour (Irwin test) at doses of proline up to 5 times the maximum dose administered 180 with Privigen in clinical studies were found except for a~~	Accepted.

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		~~slight rise of body temperature after 5 days of 181 treatment.~~	
204	1	**Comments:** "…blood-brain barrier…impermeable to exogenous proline" This is not true. The BBB is permeable to proline in rats and humans (transporter).	Not accepted. However, sentence was amended for clarity.
211	1	**Comments:** Suggest to mention high absorption after oral application here.	Not accepted.
215	1	**Comments:** Typo in study number. **Proposed change:** It should be 925/034.	Corrected.
227, 319, Table 1	1	**Comments:** Study 925/035 was conducted under GLP.	Accepted.
244	1	**Proposed change:** 4100 µmol proline/L	Added for clarity.
268	1	**Proposed change:** "Study ~~ZLB 06_009,~~ 668316…"	Not accepted. Wording consistent with the EPAR.
269	1	**Comment:** This study was conducted under GLP.	Accepted.
		Proposed change: "Study ~~CSL 07_002,~~ 668321…"	Not accepted. Wording consistent with the EPAR.

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271-272	1	**Comments:** "Toxicokinetic parameters were not determined." This is not correct. Toxicokinetic parameters were determined in these dog studies and could be added.	Text deleted
272	1	**Comments:** "(of 75 relative to the maximum clinical exposure)" This margin applies to Hizentra, not Privigen. For Privigen it would be 7.6 times maximum clinical exposure.	The sentence has been deleted.
284	1	**Comments:** Study 22196 was conducted under GLP.	Accepted.
285	1	**Comments:** Study 49196 was conducted under GLP.	Accepted.
286	1	**Comments:** Study CLE 1554-3-D5140 was conducted under GLP.	Accepted.
297, 338, Table 1	1	**Comments:** Study AA30034 was conducted under GLP.	Accepted.
299-300	1	**Proposed change:** "1449 mg/kg/day ~~are considered~~ was defined to be the NO~~A~~EL."	Partly accepted. Replaced by "1449 mg/kg/day was defined to be the NOAEL".
312	1	**Comments:** This paragraph has been described already in section 2.1. Please delete.	Not Accepted. The information in section 4.1 focuses on toxicological endpoints, while the information in line 312ff relates to toxicokinetics. There might be some overlap, but this is appropriate for reasons of comprehension.

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356, Table 1	1	**Comments:** (CSL Behring is in possession of toxicokinetic study data in the dog with Cmax up to 11100 - 16500 µmol/L which allowed a NOAEL to be defined at the respective dose. These data were provided with the Hizentra submission (sections 2.4, 2.6.4 and 2.6.5). Would it be possible to add this to the guideline?) **Proposed change:** Cmax at highest rat dose tested.	Not accepted. Only data available in the public domain can be referred to. It is already clear that the table refers to rat data.
358-365	1	**Comments:** Suggested modification of following paragraph has been adapted from the Day 121 response 39 during the Hizentra licensing process. [The deleted sentence sentences with the normal proline plasma level was repeated several times. It occurs once now on Line 365.] **Proposed change:** "Proline is a nonessential neutral amino acid and a component of nutritional proteins; the daily intake with food is about 5200 mg of which 75-80% are absorbed to the blood (Adibi et al. 1967). Up to 15.8 micromoles L-proline/kg/h are synthesized under fasting conditions (Jaksic et al. 1987), thus more than 3 g/day in an adult. Synthesis is completely inhibited after parenteral administration of high doses of L-proline (Jaksic et al.1987), indicating a feedback mechanism. ~~The normal proline plasma level is in the range of 266 ± 35 µmol/l.~~ Proline is	Accepted and references added to the list of references.

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		formed from and metabolized to glutamate. ~~However,~~ Under certain physiological conditions (severe burn, preterm neonate), i.e. when endogenous synthesis cannot meet metabolic need of proline, additional intake via dietary source is needed (conditionally indispensable) (Dietary Reference Intakes: The Essential Guide to Nutrient Requirements [11]; Wu, 2009 [35]; Wu, 2011 [3~~5~~4]). ~~The normal proline plasma 364 level is in the range of 266 ± 35 µmol/L. Proline is formed from and metabolised to glutamate.~~" Normal systemic weekly uptake of L-proline by nutrition is 364 mg/kg for adults and about 1200 mg/kg for children (1 to 5 years old) reflecting the higher protein need of children in growth (calculated from Adibi et al. 1967). These doses are in the range or above weekly proline doses applied with Privigen or Hizentra. *Adibi, SA., Seymour, JG., and Menden, E., 'The Kinetics of Amino Acid Absorption and Alteration of Plasma Composition of Free Amino Acids After Intertinal Perfusion of Amino Acid Mixtures' The American Journal of Clnincal Nutrition. January 1967, 20(1): p. 24-33.* *Jaksic, T., Wanger, DA., Burke, JF., and Young, VR., 'Plasma Proline Kinetics and the Regulation of Proline Synthesis in Man' Metabolism. November 1987, 36(11): p. 1040-1046.*	

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365-367	1	**Proposed change:** "Proline is formed from and metabolised to glutamate. Normal serum proline levels vary by age: 3–10 years 68–148 µmol/L; 6–18 years 58–324 µmol/L and > 18 years 102–336 µmol/L (Wu, 2006 [33]) or are reported to be in the range of 266 ± 35 µmol/l in adults by Druml et al.2001. " *Druml W, Heinzel G, Kleinberger G., 'Amino acid kinetics in patients with sepsis' Am J Clin Nutr 2001, 73:908-13.*	Accepted.
378	1	**Comments:** "Proline physiological serum range: 266 ± 35 µmol/l." This value occurs for the third time on this page. Delete?	Accepted.
383	1	**Proposed change:** "3- to 4-weekly intervals"	Not accepted. Corrected by "*3-4 week intervals*"
384	1	**Comments:** Requires language check.	Accepted. Text reworded.
388	1	**Proposed change:** "…1 g/kg of Privigen was administered daily for two…"	Accepted.
393	1	**Proposed change:** "… the ~~applicant~~ data showed…"	Accepted.
412	1	**Comments:** Added to align with the Privigen (IVIG) heading above. **Proposed change:** Hizentra (SCIG)	Accepted.

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418-419	1	**Proposed change:** "…returned to approximately ~~the same~~ pre-infusion levels ~~concentration as before the infusion~~."	Accepted.
421	1	**Proposed change:** "…normal range at ~~(~~450 µmol/l~~)~~."	Accepted.
422-424	1	**Proposed change:** "In the US study in 49 PID patients (ages: 5–72 y) the mean dose per week was approximately 50% higher than in the EU study, 181.5 mg/kg. The maximum proline level was 789 µmol/l~~. In comparison~~, lower than in the studies with Privigen, where median levels of 1927 µmol/l (in PID study) and 2951 µmol/l (in ITP study) were reached."	Accepted.
440	1	**Comments:** This text talks about doses of 1000 mg/kg for two consecutive days in ITP, GBS, Kawasaki. It should be made clear that for KD, 2 g/kg in a singles infusion is also approved.	Accepted.
442	1	**Comments:** "…100 mg/kg to 200 mg/kg in replacement therapy." 200 to 400 mg/kg weekly dosing is approved for CIDP treatment. This should be clearly mentioned.	Accepted.

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448-451	1	**Comments:** This paragraph should use more precise language. Please consider replacing it with: **Proposed change:** Patients with HP I and II may have seizures and other clinical symptoms. The causal link is not established (e.g. the clinical signs could be due to other metabolites affected by these enzyme deficiencies). In the absence of data establishing the safety of exposure of subject with HP I and II to additional proline, this exposure should be limited as much as possible.	Partly accepted.
486	1	**Proposed change:** "~~In sum~~ To summarize, …"	Partly accepted. Corrected by "*In summary,…*"
492, 587	1	**Comments:** CSL Behring does not agree to the term contradictory. In addition to the application route (sc vs. iv) the number of consecutive daily dosing seems to be important and explains the results without contradiction. **Proposed change:** "These ~~somewhat contradictory~~ results may possibly…"	Partly accepted.

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512-516	1	**Proposed change:** "However, that standard toxicity studies did not identify any toxic effects and the signal for neurotoxicity has been observed experimentally in a model specifically designed to study hyperprolineamia using very specific conditions. Tak~~en~~ing this into account, the amount of daily systemic synthesis of the nonessential amino acid proline in humans, the feedback inhibition of this synthesis under conditions of administration of proline by nutrition or as excipient of medicinal products, the lower or comparable doses of proline taken up after infusion of such products as compared to nutrition, and because proline is rarely used as excipient in such adequately labeled medicinal products, it was felt that a common labeling recommendation in the excipient guideline concerning neurotoxicity was not reasonable."	Accepted.
533 and 535	1	**Comments:** (The 4350 mg/kg is a NOAEL in the dog, not in the rat.) **Proposed change:** ~~4350~~ 1449 mg/kg, the highest dose that could be assessed in rats.	Accepted.
551	1	**Comments:** "While proline metabolism and excretion increase as age…" Concerning metabolism, this is not clear. Newborn have a high protein synthesis which require also high amounts of proline. Reason for increased BBB permeability at young age? Concerning excretion, there is very low excretion of proline.	Partly accepted. Text adjusted.

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572-573 578-579	1	**Proposed change:** "4 g/kg administered daily for ~~2-~~5 consecutive days or once ~~every 2-4 weeks~~ once weekly for 3 weeks there was no finding…"	Not accepted.
576	1	**Proposed change:** "…i.e. twice daily application…"	Accepted.
596	1	**Proposed change:** "…conducted with rats (SC and IV, NOAEL 1449 mg/kg) and dogs (IV, NOAEL 4350 mg/kg) of up to 28 days (~~NOAEL 4350 mg/kg~~)…"	Accepted.
599	1	**Comments:** "The effects of consistently high proline plasma levels can be seen in hereditary hyperprolinemia…" This makes a link between plasma proline levels and effects. A slight text change is proposed to indicate that this causal link isunproven, however despite the absence of evidence exposure of HP I and II patients should be minimized. This should be addressed consistently throughout the document. The genetic defects may cause these neurological abnormalities through other mechanisms.	Partly accepted. Text adjusted.
602: first bullet point.	1	**Proposed change:** "HPI is caused by an abnormality in the proline-oxidizing enzyme (POX). The POX gene (PRODH) 602 is located on chromosome 22 (22q11.21). ~~This region is deleted~~ There is a heterozygous deletion of this region in congenital malformation syndromes including velo-cardio-facial syndrome, DiGeorge Syndrome and conotruncal anomaly	Accepted.

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		face syndrome. This gene locus is also related to susceptibility to schizophrenia. The incidence of chromosome 22q11.2 deletion syndrome is ~27:100 000 live births. Approx. 50% of patients with 22q11.2 deletion have some degree of hyperprolinemia (less severe than in HPI, with homozygous deletion of the POX gene) and approx. 77% of patients with 22q11.2 deletion are immunodeficient (mainly thymic hypoplasia); antibody defects are only present in 15%. Data from European and US registries for immunodeficiencies showed that 3% of patients with DiGeorge syndrome require IgG therapy. An estimated 1675–2400 people with 22q11.2 deletion could be treated with IgG therapy in the USA. Half of these may be hyperprolinemic." There is no evidence to suggest that patients with chromosome 22q11.2 deletion syndrome, including those with DiGeorge syndrome, would be affected by transient elevations in plasma L-proline following treatment with Hizentra or Privigen. [16] Hagan 2012	

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634-637	1	**Comments:** Please consider the addition of this sentence since accumulation would only be expected if administration is more frequent than about 5 half-lives, ie daily. **Proposed change:** "As the half-life of proline is approx. 5 hours and the dosing intervals of Hizentra (low dose; weekly) and Privigen (higher dose, 3–4 weekly) should not lead to any accumulation, given an intact proline metabolism. No accumulation of proline was seen in clinical studies. Proline is eliminated from the plasma by about 50% within 2 hours after end of infusion, and more than 90% within 24 hours."	Accepted.
642	1	**Proposed change:** "In children, ~~and~~ adolescents and adults with an intact proline metabolism, …"	Accepted.
643	1	**Comments:** "…parenteral short-term single doses of a treatment containing proline as an excipient can be given at an amount of ≤ 350 mg/kg/daily." Speaking of single doses daily does not cover the labeled Kawasaki dose of 2 g IgG/kg. Why 350 mg/kg? At the approved 2g IgG/kg (Kawasaki), 575 mg proline/kg are given. No cases of proline-related toxicity have been identified from the monthly review of Privigen data over 11 years in the market. The highest tolerable proline dose in humans is not known. CSL Behring suggests not writing a maximum dose of proline here.	Partly accepted. This paragraph was reworded.

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644-646	1	**Comments:** "In children and adolescents with an intact proline metabolism, parenteral long-term repeated doses of a treatment containing proline as an excipient can be given at an amount of ~0.060 g/kg/weekly or ~250 mg/kg/monthly." CSL Behring disagrees with this entire sentence. This corresponds to a weekly dose of 400 mg Hizentra/kg bw or 200 mg Privigen/kg, which does not correspond to the clinical use of these two products which are also used in higher doses in chronic conditions. The approved CIDP Hizentra dosing is 400 mg/kg weekly. With a half-life of 5 h, proline level will be back to baseline well before 1 week, so repeated administration at weekly intervals should be similar to single dose administration. In clinical practice proline doses higher than 58 mg/kg are given at weekly intervals without any AE related to proline reported.	See above.
651	1	**Comments:** CSL Behring would like to make it clear that in the labeling HP I and II are contraindicated, not hyperprolinemia generally. **Proposed change:** "(up to 500–3700 µM, normal 266 ± 35 µmol/L)"	Accepted.

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651-654	1	**Comments:** This should apply to other proline containing products, not just the CSL Behring products. CSL Behring suggests added the last sentence for clarity in light of the above discussion. **Proposed change:** "This is in line with the labelling of the approved proline containing medical products which is contraindicated in patients with hyperprolinaemia type I and II, i.e. the use of Privigen and Hizentra (proline containing IgG medical products) is contraindicated in Patients suffering from hyperprolinaemia type I and II~~)~~." Proline containing products are not contraindicated in patients with heterozygous deletion of the POX gene, as in 22q112 deletion syndromes.	Not accepted. It is recognised that the labelling proposal maybe relatively strict for some forms of hyperprolinemia, for example in those patients with heterozygous deletion of the POX gene as in 22q112 deletion syndromes, however, an overall labelling proposal is applied for proline.
663	1	**Comments:** "… the use of Privigen and Hizentra in children (approved for children (0-18 years)…" Consider adding 'including infants and neonates'.	Not accepted. The age range is 0 to 18 years is already clear enough.
667	1	**Comments:** Typo **Proposed change:** Hizentra (~~I~~SCIg)	Corrected.

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778	1	**Comments:** "Please note that the information in the PIL related to hyperprolinaemia is not consistent with the SPC." CSL Behring is not clear what is not consistent between the SPC and the PIL. In both, patients are not to take our product if they have hyperprolinaemia type I or II.	The annex was deleted.