<15 August 2012>

Submission of comments on 'Quality Review of Documents (QRD) human product information annotated template: revision of the product information - Draft' (EMA/468498/2012)

Comments from:

Name of organisation or individual
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Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comments	Outcome (if applicable) *(To be completed by the Agency)*
	The aim of the revision of the product information (Summary of Product Characteristics, SPC and Package leaflet) is to incorporate the new provisions of the pharmacovigilance legislation into the QRD human product information template[1]. Against this background, product information should: - Allow patients and health professionals to **easily identify products "subject to additional monitoring"[2]**, using the well known **black symbol, i.e.** a black triangle pointing downwards, that systematically **precedes the brand name - in the SPC, package leaflet, as well as on primary (i.e. blisters) and secondary (i.e. box) packaging**; - Enable patients and health professionals to **easily identify whether a marketing authorisation has been granted under conditions or exceptional circumstances**; - Allow patients as well as health professionals to **identify recent clinically relevant changes** (administratively called "variations") to the product information**, in particular changes due to pharmacovigilance reasons** (i.e. these should be added **in bold** to the section on "clinical particulars" and in the package leaflet, preceded by an explanatory sentence specifying the last updating date); - Enable patients to **grasp the meaning of harm-benefit balance, by adding further** information to support health literacy (expected health benefits and potential adverse effects sorted by level of severity and frequency; - Clearly **encourage health professionals and patients to report any suspected adverse drug reactions** by describing the issues at stake.	

[1]- European Medicines Agency "Quality Review of Documents (QRD) human product information annotated template: revision of the product information" EMA/468498/2012; 12 July 2012: 15 pages.
[2]- Naming these products "under intensive monitoring" is a euphemism for "products subject to additional monitoring". In reality, the evaluation (subsequent authorisation) of these products has either been based on insufficient evidence or there are grounds for additional safety concerns/precautions.

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	The package leaflet remains the key information resource for medicine users. Patients should be encouraged not to discard the package leaflet and to keep the packaging intact. This message should be systematically inserted both on primary and secondary packaging. Regrettably, **the revision** of the product information **as proposed in the draft EMA/468498/2012 does not meet these objectives. Even worse, it misinterprets the spirit of the pharmacovigilance legislation**, which is to reduce otherwise preventable drug-induced harm. The comments below provide further detail. We hope they will be taken into consideration when writing up the final document. Concerns about creating an atmosphere of fear and worry in the population veil a rather paternalistic approach and EU health authorities' reluctance in being held accountable by EU citizens. Nevertheless, in order to be actively engaged in their own care and make informed choices, **patients and medicines users have the right to know and to understand both the benefits to be expected from a treatment as well as the harms that might arise when taking the medicine as prescribed.**	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
	Annex 1 Summary of Product Characteristics Preceding section 1 Black symbol	**Comments:** If the aim is to help patients to easily identify products under intensive monitoring, then the black symbol to be adopted should be the same as the one being used in the UK and in other EU Member States: the black triangle pointing downwards. In addition to its use before section 1 (Name of the product), the black triangle should be included on every occasion that the product is mentioned either by brand name (invented name) or by International Non-proprietary Name **(**including on primary (i.e. blisters) and secondary (i.e. box) packaging). The descriptive sentence should be clarified (please read proposed changes below). **Proposed changes[3]:** [For medicinal products subject to additional monitoring ONLY: The black symbol **(a black triangle pointing downwards) ~~and the statements should only~~ should always** appear **~~preceding section 1~~ preceding the {(Invented) name} throughout the product information.**	

[3]- Additions in ***italic and bold***, deletions ~~**crossed and in bold**~~

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		The descriptive statement should only be included before section 1, and should read as follows: <{Black symbol**: inverted black triangle**} This medicinal product is subject to additional monitoring ***due to limited*** *knowledge* ***about its adverse reactions***. Monitoring allows a faster identification of any safety ~~**information**~~ **concerns**. Healthcare professionals ~~**are encouraged**~~ ***are bound to*** report any suspected adverse reactions. See section 4.8. >	
	Annex 1 Summary of Product Characteristics 1. Name of the Medicinal Product	**Comments:** If the aim is to help patients to easily identify products under intensive monitoring, then the black symbol (black triangle pointing downwards) should appear each time the product is named either by brand name (invented name) or by International Non-proprietary Name (active substance(s)). The International Nonproprietary Name (INN) (the name of the "active substance(s)") is the real name of a medicine. The stems used in INNs help identification of pharmacological properties, mechanisms of action, etc. and help users and professionals to better recognize the drug's effects and risk of interaction with other products. In France, in line with the 2011 legislation (still	

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		awaiting implementation), prescribers will have to prescribe by INN. **Proposed changes:** For medicinal products subject to additional monitoring ONLY: [The black symbol **(a black triangle pointing downwards)** ~~**and the statements should only**~~ **should always** appear ~~**preceding section 1**~~ **preceding the {(Invented) name}** ~~in the section 1~~**all throughout the product information.**] *International Nonproprietary Name, INN* (<{Black symbol: **inverted black triangle**}>{(Invented) name, strength, pharmaceutical form})	
	Annex 1 Summary of Product Characteristics **4. Clinical particulars** 4.1 Therapeutic indications 4.2 Posology and method of administration 4.3 Contraindications 4.4 Special warnings and precautions for use 4.5 Interaction with other	**Comments:** Variations to the marketing authorisation due to pharmacovigilance reasons lead to changes in the product information. Such changes can consist of: - Restriction of therapeutic indications; - Different posology and/or adapted dosage form; - Additional contraindications; - Other special warnings and other precautions for use; - Additional interactions with other medicinal	

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	medicinal products and other forms of interaction 4.6 Fertility, pregnancy and lactation 4.7 Effects on ability to drive and use machines 4.8 Undesirable effects 4.9 Overdose	products, or other forms of interaction; - Additional cautionary messages about fertility, pregnancy and lactation; - Additional cautionary messages regarding ability to drive and use machines; - Additional unwanted effects; - Additional cautionary messages about the risk of overdose. If the aim is to enable patients as well as health professionals to **identify recent clinically relevant changes** (i.e. "variations") to the product information**, particularly when due to pharmacovigilance reasons, then these modifications should be easily noticeable.** They can be added **in bold in the section on "clinical particulars"**, preceded by an explanatory sentence with the last date of update. This would **help health professionals** to be up-to-date. This addition would prove more useful than the current administrative section "10. Date of the revision of the text" which does not provide any details on the nature of the changes made. **Proposed changes:** Add a descriptive sentence under the title section "4.	

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		Clinical particulars" stating: **"*The most recent changes made to this section relate to pharmacovigilance concerns and/or risk minimisation measures. They are presented in bold to be easily identified. (Last update: <add date>; previous updates: <add last update>; <add last update date; etc.). "*** These changes to the product information should be inserted under section "4. Clinical particulars" using **bold font**.	
	Annex 1 Summary of Product Characteristics 4. Clinical particulars **Subsection** **4.1 Therapeutic indications**	**Comments:** This section is the most important part of the SPC as it summarises the authorised therapeutic indications. Therefore, it is essential and relevant to specify here whether the marketing authorisation has been granted under conditions or exceptional circumstances, rather than burying that information at the end of the final section as it is currently the case (section "6. Contents of the pack and other information"). **Proposed changes:** Where relevant, **add the following clarification to subsection 4.1 Therapeutic indications:** ***<This medicine has been authorized under***	

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		'conditional approval'. This means that more evidence needs to be gathered about its benefits and adverse effects. ***Every year, the European Medicines Agency will review new information on this drug and will update this leaflet if needed. >*** ***<This medicine has been authorized under 'exceptional circumstances'. This means that <due to the nature of this disease (rare)> <for scientific reasons> <for ethical reasons> it has been impossible to obtain sufficient evidence on this medicine.*** ***Every year, the European Medicines Agency will review new information on this drug and will update this leaflet if needed. >***	
	Summary of Product Characteristics **4.8 Undesirable effects**	**Comments:** The list of adverse drug reactions is often long, combining different adverse reactions (both in severity and frequency, thus discouraging reading. The new sub-heading should be included at the beginning of section 4.8 to grab the readers' attention. The official wording "Adverse drug reactions", as defined in the Pharmacovigilance legislation, should be consistently used to prevent misunderstanding, misinterpretations, or confusion. The reference to the concept of harm-benefit is	

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		welcome and should not be removed. Yet, there needs to be an additional explanation on the marketing process to improve health literacy. A benefit is a material or experiential good 'thing', while a risk is a 'probability', the chance that something bad will happen. We should therefore be weighing benefit against harm, and the probability of benefit against the probability of harm. In doing that we should consider the kinds of benefit and harm, their chance of occurring, their magnitude and importance (primarily to the patient), as well as their timing and duration. We should therefore refer to the "harm-benefit" balance, duly noted with a hyphen, rather than a slash, to indicate a balance (of equal levels). The evaluation of older marketing authorisations due to safety concerns should prompt the review of the ADR information to be contained on the SPC and on the package leaflet. Package leaflets for centrally-approved medicines have brought along a positive development, the ADR section starts by describing serious events, and is then followed by the list of events (by frequency). This practice should be extended to all other medicines.	

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		In addition, the adverse drug reactions sections should contain systematically the following information: - What is an adverse event; - How is a marketing authorisation granted and how are adverse events collected in clinical trials; - Why is ADR notification important for healthcare professionals and patients; - Name and contact details of entity responsible for the collection of patient ADR reporting; - List of national authority/EMA websites with updated package leaflets; - Encourage the exchange of views between patients and healthcare professionals on the information contained in the leaflet: how to recognize a given adverse event; which risks are involved; can a side-effect be avoided? SPCs and package leaflets must be transparent about suspected ADRs as well as the follow-up of risk management plans. **Proposed changes:** **4.8 ~~Undesirable effects~~ Adverse *drug reactions*** <Paediatric population> [For ALL medicinal products: The new sub-heading should appear at the **~~end~~ beginning** of the section 4.8]	

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		Reporting of suspected adverse reactions **"*The efficacy and safety of medicinal products are tested in a relatively small population during clinical trials. Therefore, some adverse drug reactions cannot be identified. The*** reporting of suspected adverse reactions helps to gather important information ***about the medicinal product, notably its adverse effects. It enables*** the continuous monitoring of a medicinal product's harm-benefit balance. Any suspected adverse reactions should be reported via {insert information on the relevant 'national reporting system' – *details will be defined at national level*}.	
	Annex 2 Package leaflet	**Same comments as described previously:** If the aim is to help patients to easily identify products under intensive monitoring, then the black symbol (black triangle pointing downwards) should appear on each occasion that the product is mentioned, either by its brand (invented name), or by its International Non-proprietary Name (active substance(s)), <u>including on primary (i.e. blisters) and secondary (i.e. box) packaging</u>. The official wording "Adverse drug reactions", as defined in the Pharmacovigilance legislation, should be consistently used to prevent misunderstanding,	

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		misinterpretations, or confusion. **Proposed changes:** For medicinal products subject to additional monitoring ONLY: [The black symbol **(a black triangle pointing downwards)** ~~**and the statements should only**~~ **should always** be included ~~**preceding section 1**~~ **before the {(Invented) name}** ~~in the section 1~~**all throughout the product information.**] <{Black symbol**: inverted black triangle**} This medicinal product is subject to additional monitoring ***due to limited*** *knowledge* ***about its adverse reactions***. Monitoring allows a faster identification of any safety ~~**information**~~ **concerns**. You can help by reporting any ~~**side effects**~~ ***suspected adverse drug reactions*** you may suffer (See section 4)>	
	1. What is X and what it is used for	**Comments:** This section is a fundamental part of the package leaflet, as it summarises the authorised therapeutic indications. Therefore, it is essential and relevant to specify here whether the marketing authorisation has been granted under conditions or exceptional circumstances, rather than burying that information at the end of the final section as it is currently the case (section "6. Contents of the pack and other	

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		information"). **Proposed changes:** Where relevant, **add the following precisions in section 1:** ***<This medicine has been authorized under 'conditional approval'. This means that more evidence needs to be gathered about its benefits and adverse effects.*** ***Every year, the European Medicines Agency will review new information on this drug and will update this leaflet as needed. >*** ***<This medicine has been authorized under 'exceptional circumstances'. This means that <due to the nature of this disease (rare)> <for scientific reasons> <for ethical reasons> it has been impossible to obtain sufficient evidence on this medicine.*** ***Every year, the European Medicines Agency will review new information on this drug and will update this leaflet as needed. >***	
	Annexe 2 4. Possible side effects	**Same comments as above:** The official wording **"Adverse drug reactions"**, as defined in the Pharmacovigilance legislation, should be consistently used rather than "**side effects"** to prevent misinterpretations or confusion.	

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		Proposed changes: **4. ~~Side effects~~ Suspected adverse drug reactions** **Reporting of ~~side effects~~ suspected adverse drug reactions** If you **~~get~~ suspect** of any **~~side effects~~** ***adverse reactions***, talk to your <doctor> <or> <, > <pharmacist> <or nurse>. This includes any possible **~~side effects~~ adverse reactions** not listed in this leaflet. You can also report any **~~side effects~~** ***adverse reactions*** directly to the national reporting system online at {insert link to the relevant 'national reporting system website' - *details will be defined at national level*}; or you can report by {insert alternative ways of reporting - *details will be defined at national level*}. When reporting **~~side effects~~ an adverse reaction** you are helping **~~provide more information on the safety of this medicine~~** to build the knowledge around the harms caused by this medicine and protecting others from experiencing the same in the future.	
	<Read all of this leaflet carefully (…)> messages	**Comments:** Variations to the marketing authorisation due to pharmacovigilance reasons lead to changes in the product information. If the aim is to enable patients as well as health professionals to **identify recent clinically relevant**	

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		changes (i.e. "variations") to the product information**, particularly when due to pharmacovigilance reasons, then these modifications should be easily noticeable.** They can be added **in bold in the section on "clinical particulars"**, preceded by an explanatory sentence with the last date of update. **<Read all of this leaflet carefully (…)>** + the last update date It would be of great **help to patients** to identify new developments in their treatments, particularly in chronic conditions. **Proposed changes:** Add an explanatory sentence as part as the **<Read all of this leaflet carefully (…)> message** as follows: <**Read all of this leaflet carefully before you start <taking> <using> this medicine as it contains important information.** - Keep this leaflet. You may need to read it again. - If you have any further questions, ask your <doctor> <or> <pharmacist> <or nurse>. <- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours. >	

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		- If you get any ~~**side effects**~~ ***adverse reactions***, talk to your <doctor> <, > <or> <pharmacist> <or nurse>. This includes any possible ~~**side effects**~~ ***adverse reactions*** not listed in this leaflet>. See section 4. - ***"The most recent changes made to this package leaflet are inserted in bold for easier identification. (Last update: <add date>; previous updates: <add about last update date>; etc.). "*** Any changes due to pharmacovigilance concerns or risk minimisation measures should be inserted in bold.	
	6. Content of the pack and other information	**Comments:** The pharmacovigilance legislation underlined the need to increase awareness among EU citizens and patients about the existing information web portals and resources from health authorities. This measure was intended to avoid "disguised direct-to-consumer advertising", whereby patients could be redirected to websites of Marketing Authorisation Holders' containing information of promotional nature, particularly on prescription-only medicines. **Proposed changes:** **Start section "6. Content of the pack and other information" by inserting the following information:**	

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		<Other sources of information> Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu. <There are also links to other websites about rare diseases and treatments. > <This leaflet is available in all EU/EEA languages on the European Medicines Agency website. > **And then add the subsections:** - What X contains - What X looks like and contents of the pack - Marketing authorisation holder and Manufacturer address - This leaflet was last revised in <{MM/YYYY}> <{month YYYY}. >	