



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 2-5 May 2017 PRAC meeting

This document provides an overview of the recommendations adopted by the Pharmacovigilance Risk Assessment Committee (PRAC) on the signals discussed during the meeting of 2-5 May 2017 (including the signal European Pharmacovigilance Issues Tracking Tool [EPITT]¹ reference numbers).

PRAC recommendations to provide supplementary information are directly actionable by the concerned marketing authorisation holders (MAHs). PRAC recommendations for regulatory action (e.g. amendment of the product information) are submitted to the Committee for Medicinal Products for Human Use (CHMP) for endorsement when the signal concerns Centrally Authorised Products (CAPs), and to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) for information in the case of Nationally Authorised Products (NAPs). Thereafter, MAHs are expected to take action according to the PRAC recommendations.

When appropriate, the PRAC may also recommend the conduct of additional analyses by the Agency or Member States.

MAHs are reminded that in line with Article 16(3) of Regulation No (EU) 726/2004 and Article 23(3) of Directive 2001/83/EC, they shall ensure that their product information is kept up to date with the current scientific knowledge including the conclusions of the assessment and recommendations published on the European Medicines Agency (EMA) website (currently acting as the EU medicines webportal).

For CAPs, at the time of publication, PRAC recommendations for update of product information have been agreed by the CHMP at their plenary meeting (15-18 May 2017) and corresponding variations will be assessed by the CHMP.

For nationally authorised medicinal products, it is the responsibility of the National Competent Authorities (NCAs) of the Member States to oversee that PRAC recommendations on signals are adhered to.

Variations for CAPs are handled according to established EMA procedures. MAHs are referred to the available [guidance](#). Variations for NAPs (including via mutual recognition and decentralised procedures) are handled at national level in accordance with the provisions of the Member States.

¹ The relevant EPITT reference number should be used in any communication related to a signal.



The timeline recommended by PRAC for submission of variations following signal assessment is applicable to both innovator and generic medicinal products, unless otherwise specified.

For procedural aspects related to the handling of PRAC recommendations on signals (e.g. submission requirements, contact points, etc.) please refer to the [Questions and Answers on signal management](#).

1. Recommendations for update of the product information

1.1. Brentuximab vedotin – Cytomegalovirus (CMV) reactivation²

Authorisation procedure	Centralised
EPITT No	18789
PRAC rapporteur(s)	Sabine Straus (NL)
Date of adoption	5 May 2017

Recommendation

Having considered the available evidence in EudraVigilance, clinical trials and in the literature, and the known association of brentuximab vedotin with infections, the PRAC has agreed that the MAH(s) of brentuximab vedotin-containing medicinal products should submit a variation within 2 months, to amend the product information as described below (new text underlined):

Summary of product characteristics

4.4. Special warnings and precautions for use

Serious infections and opportunistic infections

Serious infections such as pneumonia, staphylococcal bacteraemia, sepsis/septic shock (including fatal outcomes) and herpes zoster, Cytomegalovirus (CMV) (reactivation) and opportunistic infections such as Pneumocystis jiroveci pneumonia and oral candidiasis have been reported in patients treated with brentuximab vedotin. Patients should be carefully monitored during treatment for the emergence of possible serious and opportunistic infections.

4.8. Undesirable effects

Infections and infestations

Frequency 'uncommon': Cytomegalovirus infection or reactivation

Package leaflet

4. Possible side effects

Uncommon side effects (affects less than 1 in 100 people)

- new or recurring cytomegalovirus (CMV) infection

² Translations in all official EU languages of the new product information adopted by PRAC are also available to MAHs on the EMA website.

1.2. Insulin (pre-filled pens and cartridges): insulin aspart; insulin bovine; insulin degludec; insulin degludec, insulin aspart; insulin degludec, liraglutide; insulin detemir; insulin glargine; insulin glulisine; insulin human (rDNA); insulin human, insulin isophane; insulin lispro; insulin porcine – Potential increased risk of medication error associated with pre-filled pens and cartridges presentations, leading to inadequate diabetes control

Authorisation procedure	Centralised and non-centralised
EPITT No	18893
PRAC rapporteur(s)	Julie Williams (UK)
Date of adoption	5 May 2017

Recommendation [see also section 2]

Having considered the available evidence, including the Risk minimisation strategy for high-strength and fixed-combination insulin products (EMA/686009/2014, 23 October 2015), the PRAC has agreed the following:

Changes to the marketing authorisation are required for those products where the wording in section 4.2, 4.4 or 6.6 of the summary of product characteristics and/or section 3 of the package leaflet is not in accordance with the Risk minimisation strategy for high-strength and fixed-combination insulin products (EMA/686009/2014, 23 October 2015). In particular, the MAHs for the high strength and fixed combination insulin-containing products (please refer to the list of products in Appendix A), sanofi-aventis Deutschland GmbH and Novo Nordisk A/S, should submit a variation within 60 days to align the wording about medication errors related to misuse of insulin extraction from pen using a syringe.

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Acetazolamide	Acute generalised exanthematous pustulosis (AGEP) (18892)	Ulla Wändel Liminga (SE)	Supplementary information requested (submission by 26 July 2017)	Mercury Pharmaceuticals Ltd
Amoxicillin	Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome (18802)	Jan Neuhauser (AT)	Supplementary information requested (submission by 1 June 2017)	GlaxoSmithKline

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Azithromycin; clarithromycin; erythromycin; roxithromycin	Acute generalised exanthematous pustulosis (AGEP) (18891)	Almath Spooner (IE)	Supplementary information requested (submission by 26 July 2017)	Sigma-Tau Industrie Farmaceutiche Riunite S.p.A.; Generics [UK] Limited; Amdipharm Limited; Sanofi-Aventis France
Cladribine	Progressive multifocal leukoencephalopathy (PML) (18875)	Patrick Batty (UK)	Supplementary information requested (submission by 26 July 2017)	Janssen-Cilag; Lipomed GmbH; Mylan; Instytut Biotechnologii i Antybiotyków
Insulin (pre-filled pens and cartridges): see list of concerned brand names in Appendix B	Potential increased risk of medication error associated with pre-filled pens and cartridges presentations, leading to inadequate diabetes control (18893)	Julie Williams (UK)	Supplementary information requested (submission by 26 July 2017) <i>[see also section 1]</i>	Eli Lilly Regional Operations GmbH; Novo Nordisk A/S; Sanofi-aventis Deutschland GmbH

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Pirfenidone	Colitis (18793)	Julie Williams (UK)	Monitor in PSUR	Roche Registration Limited

Appendix A

1. Insuman Implantable 400 IU/ml solution for infusion (sanofi-aventis Deutschland GmbH)
2. Toujeo 300 units/ml solution for injection in a pre-filled pen (sanofi-aventis Deutschland GmbH)
3. Tresiba 200 units/mL solution for injection in pre-filled pen (Novo Nordisk A/S)
4. Ryzodeg 100 units/mL solution for injection in pre-filled pen, Ryzodeg 100 units/mL solution for injection in cartridge (Novo Nordisk A/S)
5. Xultophy 100 units/ml insulin degludec + 3.6 mg/mL liraglutide solution for injection in a pre-filled pen (Novo Nordisk A/S)

Appendix B

1. ABASAGLAR 100 units/mL solution for injection in cartridge (insulin glargine), Eli Lilly Regional Operations GmbH
2. Actrapid 100 IU/ml solution for injection in cartridge: Penfill, InnoLet, FlexPen (human insulin), Novo Nordisk A/S
3. Apidra 100 Units/ml, solution for injection in a cartridge (insulin glulisine), sanofi-aventis Deutschland GmbH
4. Apidra 100 Units/ml solution for injection in a cartridge for OptiClik insulin glulisine sanofi-aventis Deutschland GmbH
5. Insulin Human Winthrop Rapid 100 IU/ml solution for injection in a cartridge (human insulin), sanofi-aventis Deutschland GmbH
6. Insulin Human Winthrop Basal 100 IU/ml suspension for injection in a cartridge (human insulin), sanofi-aventis Deutschland GmbH
7. Insulin Human Winthrop 100 IU/ml suspension for injection in a cartridge: Comb 15, Comb 25, Comb 30, Comb 50 (human insulin), sanofi-aventis Deutschland GmbH
8. Insulin Human Winthrop Infusat 100 IU/ml solution for injection in a vial, Insulin Human Winthrop Infusat 100 IU/ml solution for injection in a cartridge (human insulin), sanofi-aventis Deutschland GmbH
9. Insuman Rapid 100 IU/ml solution for injection in a cartridge (human insulin), sanofi-aventis Deutschland GmbH
10. Insuman Rapid 100 IU/ml solution for injection in a cartridge for OptiClik (human insulin), sanofi-aventis Deutschland GmbH
11. Insuman Basal 100 IU/ml suspension for injection in a cartridge (human insulin), sanofi-aventis Deutschland GmbH
12. Insuman Basal 100 IU/ml suspension for injection in a cartridge for OptiClik (human insulin), sanofi-aventis Deutschland GmbH
13. Insuman 100 IU/ml suspension for injection in a cartridge: Comb 15, Comb 25, Comb 30, Comb 50 (human insulin), sanofi-aventis Deutschland GmbH
14. Insuman 100 IU/ml suspension for injection in a cartridge for OptiClik: Comb 15, Comb 25, Comb 30, Comb 50 (human insulin), sanofi-aventis Deutschland GmbH
15. Insuman Infusat 100 IU/ml solution for injection in a vial (human insulin), sanofi-aventis Deutschland GmbH
16. Insuman Infusat 100 IU/ml solution for injection in a cartridge (human insulin), sanofi-aventis Deutschland GmbH
17. Lantus 100 units/ml solution for injection in a cartridge (insulin glargine), sanofi-aventis Deutschland GmbH
18. Lantus 100 units/ml solution for injection in a cartridge for OptiClik (insulin glargine), sanofi-aventis Deutschland GmbH

19. NovoRapid 100 units/ml solution for injection in vial, NovoRapid Penfill 100 units/ml solution for injection in cartridge, NovoRapid 100 units/ml solution for injection in pre-filled pen: FlexPen, FlexTouch, InnoLet, NovoRapid PumpCart 100 units/ml solution for injection in cartridge (insulin aspart), Novo Nordisk A/S
20. Toujeo 100 units/ml solution for injection in a cartridge (insulin glargine), sanofi-aventis Deutschland GmbH
21. Toujeo 100 units/ml solution for injection in a cartridge for OptiClik (insulin glargine), sanofi-aventis Deutschland GmbH