28 January 2016
EMA/PRAC/1275/2016
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the PRAC meeting of 11-14 January 2016

This document provides an overview of the recommendations adopted by the Pharmacovigilance Risk Assessment Committee (PRAC) on the signals discussed during the meeting of 11-14 January 2016 (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 (25-28 January 2016) 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.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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[2]

1.1. Oxybutynin – Psychiatric disorders

Authorisation procedure	Centralised
EPITT No	18342
PRAC rapporteur(s)	Veerle Verlinden (BE)
Date of adoption	14 January 2016

Recommendation

Having considered the responses submitted from the marketing authorisation holder (MAH) of Kentera (Nicobrand), the evidence from clinical trials and plausible biological mechanism, as well as the information received from the European Medicines Agency's Paediatric Committee, the PRAC has agreed that the MAHs of transdermal (patch, gel in sachet, metering pump) oxybutynin containing products should submit a variation within 2 months, to amend the product information as described below.

In regard to the association between transdermal oxybutynin and depression, there is not enough evidence to conclude on a possible causal relationship and therefore the MAH should continue to monitor this event as part of routine safety surveillance.

Recommended amendment to the Product Information

[New text underlined; Current text to be deleted is struck through]

Summary of Product Characteristics

- **Applicable to all formulations: Kentera 3.9 mg / 24 hours transdermal patch, Kentera 90.7 mg/g gel in sachet and Kentera 90.7 mg/g gel in a metering pump**

4.2 Posology and method of administration

[…] Elderly population

There is no dose adjustment necessary in this population. Kentera should be used with caution in elderly patients, who may be more sensitive to the effects of centrally acting anticholinergics and exhibit differences in pharmacokinetics (see section 4.4).

[…] Paediatric population

The safety and efficacy of Kentera in the paediatric population has not been established. Kentera is not recommended for use in the paediatric population. Currently available data are described in section 4.8 but no recommendation on a posology can be made.

~~There is no experience in children~~

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

4.4 Special warnings and precautions for use

[…] Kentera should be used with caution in elderly patients, who may be more sensitive to the effects of centrally acting anticholinergics and exhibit differences in pharmacokinetics.

Psychiatric and CNS anticholinergic events like sleep disorders (e.g. insomnia) and cognitive disorders have been associated with oxybutynin use, especially in elderly patients. Caution should be exercised when oxybutynin is administrated concomitantly with other anticholinergic medicines (see also section 4.5). If a patient experiences such events, drug discontinuation should be considered.

Other psychiatric events implying an anticholinergic mechanism have been reported during post-marketing use (see section 4.8). […]

4.8 Undesirable effects

[…] Tabulated list of adverse reactions

Adverse reactions from phase 3 and 4 clinical studies are listed below by system organ class and frequency grouping. Frequencies are defined as: 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); very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Post-marketing adverse reactions not seen in clinical trials are also included.

[…]

MedDRA System Organ Class	**Incidence**	**Adverse reactions**
Psychiatric disorders	Uncommon	Anxiety, confusion, nervousness, agitation, insomnia
	Rare	Panic reaction#, delirium#, hallucinations#, disorientation#
Nervous system disorders	Rare	Memory impairment#, amnesia#, lethargy#, disturbance in attention#

[…]

post-marketing adverse reactions from post-marketing reports only (not seen in clinical trials), with the frequency category estimated from clinical trial safety data, and reported in association with oxybutynin topical use (anticholinergic class effects).

Adverse reactions known to be associated with anticholinergic therapy, such as oxybutynin, are anorexia, vomiting, reflux oesophagitis, decreased sweating, heat stroke, decreased lacrimation, mydriasis, tachycardia, arrhythmia, disorientation, poor ability to concentrate, fatigue, nightmares, restlessness, convulsion, intraocular hypertension and induction of glaucoma, confusion, anxiety, paranoia, hallucination, photosensitivity, erectile dysfunction.

Paediatric population

During post-marketing use in this age group, cases of hallucinations (associated with anxiety manifestations) and sleep disorders correlated with oxybutynin have been reported. Children may be more sensitive to the effects of the product, particularly the CNS and psychiatric adverse reactions.

[…]

- **Applicable to Kentera 3.9 mg / 24 hours transdermal patch only**

4.8 Undesirable effects

[…]

MedDRA System Organ Class	Incidence	Adverse reactions
Nervous system disorders	Common	Headache, somnolence
Respiratory, thoracic and mediastinal disorders	Uncommon	Rhinitis
General disorders and administration site conditions	Common	[…], ~~headache~~, ~~Somnolence~~
	Uncommon	~~Rhinitis~~

Package leaflet

- **Applicable to all formulations: Kentera 3.9 mg / 24 hours transdermal patch, Kentera 90.7 mg/g gel in sachet and Kentera 90.7 mg/g gel in a metering pump**

4. POSSIBLE SIDE EFFECTS
[…]

Uncommon side effects:

[…]

- anxiety

- confusion

- nervousness

- agitation

- difficulty in sleeping

[…]

Rare side effects:

- panic reaction

- mental confusion

- hallucinations

- disorientation

- memory impairment

- loss of memory

- abnormal tiredness

- poor concentration

[…]

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Cisplatin	Peripheral arterial thromboembolic events (ATEs) and arterial occlusion (18560)	Doris I. Stenver (DK)	Supplementary information requested (submission by 10/03/2016)	Ebewe Pharma; Pfizer/Pharmacia
Cytarabine	Benign intracranial hypertension (18533)	Rafe Suvarna (UK)	Supplementary information requested (submission by 10/03/2016)	Pacira Ltd
Dapagliflozin; dapagliflozin, metformin	Pancreatitis (18558)	Qun-Ying Yue (SE)	Supplementary information requested (submission by 10/03/2016)	AstraZeneca AB
Gefitinib	Pneumatosis intestinalis (18575)	Ulla Wändel Liminga (SE)	Supplementary information requested (submission by 10/03/2016)	AstraZeneca AB
Levetiracetam (oral solution)	Medication errors associated with accidental overdoses (10519)	Veerle Verlinden (BE)	Supplementary information requested (submission by 10/03/2016)	UCB Pharma SA
Natalizumab	Necrotising retinitis (18605)	Brigitte Keller-Stanislawski (DE)	Supplementary information requested (submission by 10/03/2016)	Biogen Idec Ltd
Quinine	Increased mortality risk in heart failure patients with/without concomitant use of beta-blockers (18529)	Almath Spooner (IE)	Supplementary information requested (submission by 10/03/2016)	Sanofi; Takeda Pharma A/S
Warfarin	Calciphylaxis (18545)	Torbjörn Callreus (DK)	Supplementary information requested (submission by 10/03/2016)	Takeda; Bristol-Myers Squibb

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Loratadine	QT prolongation and Torsade de Pointe (18576)	Jean-Michel Dogné (BE)	No action at this stage	Not applicable
Methotrexate	Progressive multifocal leukoencephalopathy (PML), JC virus infection (18473)	Doris I. Stenver (DK)	Keep under close monitoring	MAHs of methotrexate containing products
Paracetamol; phenylephrine	Pharmacokinetic drug interaction: increased bioavailability of phenylephrine when co-administered with paracetamol (18474)	Veerle Verlinden (BE)	Routine pharmacovigilance	MAHs of paracetamol containing and phenylephrine containing products
Peginterferon alfa-2a	Guillain-Barré syndrome (GBS) (18402)	Qun-Ying Yue (SE)	Routine pharmacovigilance	Roche Registration Limited
Recombinant Factor VIII: antihemophilic factor (recombinant); moroctocog alfa; octocog alfa	Inhibitor development in previously untreated patients (18134)	Brigitte Keller-Stanislawski (DE)	No action at this stage	Bayer Pharma AG, Baxter AG, Pfizer Limited, various
Saxagliptin; Saxagliptin, metformin	Acute kidney injury (18379)	Menno van der Elst (NL)	Assess results of Post Authorisation Safety Study (CV181157 ST)	AstraZeneca AB
Thioctic acid	Insulin autoimmune syndrome (18406)	Marina Dimov Di Giusti (HR)	No action for MAHs of homeopathic products	Biologische Heilmittel Heel GmbH