EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

PRAC feedback to working parties

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25 September 2019

Pharmacovigilance Risk Assessment Committee
Representatives from each member states
+ 6 independent experts +

Members representing healthcare professionals

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Pharmaceutical Group of the European Union (PGEU)

Alternate

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Members representing patients' organisations

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European Federation of Neurogical Associations (EFNA)

Alternate

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EURORDIS - Rare Diseases Europe

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PRAC statistics: September 2019

19 Assessments of safety signals for medicines

- 10 Started
- 9 Ongoing and concluded

105 Periodic safety update reports (PSURs) single assessments

- 73 Recommendations for centrally authorised medicines only
- 29 Recommendations for nationally authorised medicines only
- 3 Recommendations for PSURs including both centrally and nationally authorised medicines

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- 20 led to a change in the product information
- 85 led to no changes

61 Risk management plans (RMPs) for centrally authorised medicines

- 6 RMPs reviewed for new medicines
- 55 RMPs reviewed for authorised medicines

28 Post-authorisation safety studies (PASSs)

- 8 Protocols for imposed studies reviewed
- 15 Protocols for non-imposed studies reviewed
- 0 Results from imposed studies reviewed
- 5 Results from non-imposed studies reviewed

1 Referral

- 1 Referral started for Picato

PRAC minutes | PRAC recommendations on safety signals | Outcomes of PSUSAs

Highlight on 4 procedures

Under evaluation

- Referral on 5-FU and others associated products
- Restriction in use of Xeljanz

Completed procedures

- Referral on Quinolones and Fluoroquinolones
- Referral on Methotrexate containing medicines

Fluorouracil and fluorouracil related substances (capecitabine, tegafur and flucytosine) containing medicinal products - Under evaluation

Article 31 referral (This type of referral is triggered when the interest of the Union is involved, following concerns relating to the quality, safety or efficacy of a medicine or a class of medicines.)

Centrally and nationally authorised products (mixed)

Start date - 15/03/2019

Fluorouracil (given by injection), capecitabine and tegafur are **cancer medicines**, whereas topical (applied to the skin) fluorouracil is used for various **skin conditions** and flucytosine is a medicine used in **severe fungal infections**.

PRAC feedback to working parties, 25 September 2019

It is known that some patients lack a working enzyme called **dihydropyrimidine dehydrogenase (DPD)** which is needed to break down fluorouracil. Build-up of high levels of fluorouracil can lead to **severe and life-threatening side effects**. Patients with a complete deficiency of DPD should therefore not be given fluorouracil, or medicines that can form it in the body.

EMA will assess the available data in relation to existing **screening methods to detect DPD deficiency** and recommend whether any changes are needed to the way these medicines are used in order to ensure their safe use.

Xeljanz (tofacitinib) - under evaluation

Article 20 procedure (This type of procedure is triggered for medicines that have been authorised via the centralised procedure in case of quality, safety or efficacy issues.)

Restrictions (temporary) in use of Xeljanz while EMA reviews **risk of blood clots in lungs**

Xeljanz is currently authorised for the treatment of **rheumatoid arthritis, psoriatic arthritis and severe ulcerative colitis**.

An ongoing study in patients with rheumatoid arthritis showed an increased risk of blood clots in the lungs and death when the **10 mg twice daily dose** was used, which is double the recommended dose for rheumatoid arthritis.

EMA's safety committee (PRAC) is recommending that doctors must not prescribe the 10 mg twice daily dose of Xeljanz (tofacitinib) in patients who are at **high risk** of blood clots in the lungs.

The new advice means that, since 10 mg is the only recommended starting dose for ulcerative colitis, patients with this condition who are at high risk of blood clots must not be started on Xeljanz […] or must be **switched to alternative treatments**.

The PRAC will now carry out a **review of all available evidence**, and **updated guidance** will be provided to patients and healthcare professionals once the review is concluded.

Article 31 referral – Quinolones and Fluoroquinolones
New restrictions to avoid potentially permanent side effects.

Restrictions on the use of fluoroquinolone antibiotics will mean that they **should not** be used:

- to treat **infections that might get better without treatment** or are not severe (such as throat infections);
- to treat **non-bacterial infections**, e.g. non-bacterial (chronic) prostatitis;
- for **preventing** traveller's diarrhoea or **recurring lower urinary tract infections** (urine infections that do not extend beyond the bladder);
- to treat **mild or moderate bacterial infections** unless other antibacterial medicines commonly recommended for these infections cannot be used.

Article 31 referral – Methotrexate containing medicines
New measures to avoid dosing errors

Misunderstandings of the dosing schedule have led to **patients** taking the medicine **daily instead of weekly**, with serious consequences, including fatalities.

Additional measures to reduce dosing errors include:

- restricting **who can prescribe** these medicines,
- making **warnings** on the packaging **more prominent**
- **providing educational materials** for patients and healthcare professionals
- **tablets** for weekly use will be **provided in blister packs** and not in bottles or tubes