EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee (PRAC)

# New product information wording – Extracts from PRAC recommendations on signals

Adopted at the 8-11 July 2024 PRAC

The product information wording in this document is extracted from the document entitled 'PRAC recommendations on signals' which contains the whole text of the PRAC recommendations for product information update, as well as some general guidance on the handling of signals. It can be found on the webpage for PRAC recommendations on safety signals (in English only).

New text to be added to the product information is underlined. Current text to be deleted is ~~struck through~~.

## 1. Acetazolamide – Pulmonary oedemas (EPITT no 20050)

*Taking into account the already existing wording in some nationally authorised products, the text may need to be adapted by marketing authorisation holders to individual products.*

**Summary of product characteristics**

4.4 Special warnings and precautions for use

Non-cardiogenic pulmonary oedema

Severe cases of non-cardiogenic pulmonary oedema have been reported after taking acetazolamide, also after a single dose (see section 4.8). Non-cardiogenic pulmonary oedema typically developed within minutes to hours after acetazolamide intake. Symptoms included dyspnoea, hypoxia, and respiratory insufficiency. If non-cardiogenic pulmonary oedema is suspected, acetazolamide should be withdrawn, and supportive treatment should be given. Acetazolamide should not be administered to patients who previously experienced non-cardiogenic pulmonary oedema following acetazolamide intake.

[1] Expected publication date. The actual publication date can be checked on the webpage dedicated to PRAC recommendations on safety signals.

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4.8 Undesirable effects

Respiratory, thoracic and mediastinal disorders

Frequency 'not known': Non-cardiogenic pulmonary oedema

**Package leaflet**

2. What you need to know before you take [product name]

Warnings and precautions

Talk to your doctor before taking [product name]:

• If you experienced lung or breathing problems (fluid in the lungs) following acetazolamide intake in the past.

[…]

If you develop shortness of breath or difficulty breathing after taking [product name], seek medical attention immediately (see also section 4).

4. Possible side effects

Contact a doctor immediately if you experience any of the following symptoms:

• If you develop shortness of breath or difficulty breathing. These can be symptoms of accumulation of fluid in the lungs (pulmonary oedema). The frequency of this side effect cannot be estimated from the available data (not known).

# 2. Bumetanide – Toxic epidermal necrolysis and Stevens-Johnson syndrome (EPITT no 20033)

*Taking into account the already existing wording in some nationally authorised products, the text may need to be adapted by marketing authorisation holders to individual products.*

**Summary of product characteristics**

4.4 Special warning and precautions for use

Toxic epidermal necrolysis (TEN) and Stevens Johnson syndrome (SJS), which can be life-threatening or fatal, have been reported in relation to non-antibiotic sulphonamide containing products, including bumetanide. Patients should be advised of the signs and symptoms of SJS and TEN and closely monitored for those. If signs and symptoms suggestive of these reactions appear, bumetanide should be withdrawn, and an alternative therapy should be considered. If the patient has developed a serious reaction such as SJS or TEN, with the use of bumetanide, treatment with bumetanide must not be restarted in this patient at any time.

4.8 Undesirable effects

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), have been reported in association with bumetanide (see section 4.4).

Under SOC Skin and subcutaneous tissue disorders with frequency "Not known":

Stevens-Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN)

**Package leaflet**

2. What you need to know before you take [Product name]

Warnings and precautions

Talk to your doctor or pharmacist before taking [Product name]

- If you have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after taking [Product name] or other sulphonamides, e.g., loop diuretics.
- If you have severe liver problems.
- […]

Serious skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported in association with [Product name] treatment. Stop using [Product name] and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4.

4. Possible side effects

Important side effects to look out for.

Stop using [Product name] and seek medical attention immediately if you notice any of the following symptoms:

- reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms [Stevens-Johnson syndrome, toxic epidermal necrolysis].

~~Although allergic reactions are not known to happen with [Product name], it could happen with any medicine.~~ You must get medical help straight away if you have any of the following symptoms. You may be having a severe allergic reaction. […]

# 3. Glofitamab – Immune effector cell-associated neurotoxicity syndrome (EPITT no 20058)

**Summary of product characteristics**

4.2 Posology and method of administration

Columvi must only be administered under the supervision of a healthcare professional experienced in the diagnosis and treatment of cancer patients and who has access to appropriate medical support to manage severe reactions associated with cytokine release syndrome (CRS) and Immune effector cell-associated neurotoxicity syndrome (ICANS).

Posology
*Patient monitoring*
[…]

All patients must be monitored for signs and symptoms of CRS and immune effector cell-associated neurotoxicity syndrome (ICANS) following Columvi administration.

All patients must be counselled on the risk, signs and symptoms of CRS and ICANS and advised to contact the healthcare provider immediately should they experience signs and symptoms of CRS and/or ICANS at any time (see section 4.4).

**Table 3. ASTCT CRS grading and CRS management guidance**

| **Grade**[1] | **CRS management** | **For next scheduled Columvi infusion** |
|---|---|---|
| **Grade 1**<br><br>Fever ≥ 38 °C | If CRS occurs during infusion:<br>• Interrupt infusion and treat symptoms<br>• Restart infusion at slower rate when symptoms resolve<br>• If symptoms recur, discontinue current infusion<br>If CRS occurs post-infusion:<br>• Treat symptoms<br>If CRS lasts more than 48 h after symptomatic management:<br>• Consider corticosteroids[3]<br>• Consider tocilizumab[4]<br>For CRS with concurrent ICANS, refer to Table 4. | • Ensure symptoms are resolved for at least 72 hours prior to next infusion<br>• Consider slower infusion rate[2] |

*[changes only shown for Grade 1 CRS above; the same proposed text* For CRS with concurrent ICANS, refer to Table 4. *is to be included for Grade 2, Grade 3, and Grade 4 CRS in the final updated EU product information.]*

*Management of Immune effector cell-associated neurotoxicity syndrome (ICANS)*

At the first sign of ICANS, based on the type and severity consider supportive therapy, neurology evaluation, and withholding Columvi (see Table 4). Rule out other causes of neurologic symptoms. If ICANS is suspected, it should be managed according to the recommendations in Table 4.

**Table 4. ICANS grading and management guidance**

<table>
<tr><th rowspan="2">Grade[1]</th><th rowspan="2">Presenting symptoms[2]</th><th colspan="2">ICANS management</th></tr>
<tr><th>Concurrent CRS</th><th>No concurrent CRS</th></tr>
<tr><td>Grade 1</td><td>ICE[3] score 7-9<br><br>Or depressed level of consciousness[4]: awakens spontaneously</td><td>• Manage CRS per Table 3.<br>• Monitor neurologic symptoms and consider neurology consultation and evaluation, per physician discretion.</td><td>• Monitor neurologic symptoms and consider neurology consultation and evaluation, per physician discretion.</td></tr>
<tr><td></td><td></td><td colspan="2">Withhold Columvi until ICANS resolves.<br><br>Consider non-sedating, anti-seizure medicinal products (e.g., levetiracetam) for seizure prophylaxis.</td></tr>
<tr><td>Grade 2</td><td>ICE[3] score 3-6<br><br>Or depressed level of consciousness[4]: awakens to voice</td><td>• Administer tocilizumab per Table 3 for management of CRS.<br>• If no improvement after starting tocilizumab, administer dexamethasone[5] 10 mg intravenously every 6 hours if not already taking other corticosteroids. Continue dexamethasone use until resolution to Grade 1 or less, then taper.</td><td>• Administer dexamethasone[5] 10 mg intravenously every 6 hours.<br>• Continue dexamethasone use until resolution to Grade 1 or less, then taper.</td></tr>
<tr><td></td><td></td><td colspan="2">Withhold Columvi until ICANS resolves.<br><br>Consider non-sedating, anti-seizure medicinal products (e.g., levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists for further evaluation, as needed</td></tr>
<tr><td>Grade 3</td><td>ICE[3] score 0-2<br><br>Or depressed level of consciousness[4]: awakens only to tactile stimulus;<br><br>Or seizures[4], either:<br>• any clinical seizure, focal or generalised that resolves rapidly, or<br>• non-convulsive seizures on electroencephalogram (EEG) that resolve with intervention;<br><br>Or raised intracranial pressure: focal/local oedema on neuroimaging[4]</td><td>• Administer tocilizumab per Table 3 for management of CRS.<br>• In addition, administer dexamethasone[5] 10 mg intravenously with the first dose of tocilizumab, and repeat dose every 6 hours, if not already taking other corticosteroids. Continue dexamethasone use until resolution to Grade 1 or less, then taper.</td><td>• Administer dexamethasone[5] 10 mg intravenously every 6 hours.<br>• Continue dexamethasone use until resolution to Grade 1 or less, then taper.</td></tr>
<tr><td></td><td></td><td colspan="2">Withhold Columvi until ICANS resolves.<br><br>For Grade 3 ICANS events which do not improve within 7 days, consider permanently discontinuing Columvi.<br><br>Consider non-sedating, anti-seizure medicinal products (e.g., levetiracetam) for seizure prophylaxis.</td></tr>
</table>

<table>
<tr><th>Grade[1]</th><th>Presenting symptoms[2]</th><th colspan="2">ICANS management</th></tr>
<tr><th></th><th></th><th>Concurrent CRS</th><th>No concurrent CRS</th></tr>
<tr><td></td><td></td><td colspan="2">Consider neurology consultation and other specialists for further evaluation, as needed.</td></tr>
<tr><td>Grade 4</td><td>ICE[3] score 0<br><br>Or depressed level of consciousness[4], either:<br>• patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or<br>• stupor or coma;<br><br>Or seizures[4], either:<br>• life-threatening prolonged seizure (> 5 minutes), or<br>• repetitive clinical or electrical seizures without return to baseline in between;<br><br>Or motor findings[4]:<br>• deep focal motor weakness such as hemiparesis or paraparesis;<br><br>Or raised intracranial pressure/cerebral oedema[4], with signs/symptoms, such as:<br>• diffuse cerebral oedema on neuroimaging, or<br>• decerebrate or decorticate posturing, or<br>• cranial nerve VI palsy, or<br>• papilloedema, or<br>• Cushing’s triad</td><td>• Administer tocilizumab per Table 3 for management of CRS.<br>• As above, or consider administration of methylprednisolone 1 000 mg per day intravenously with first dose of tocilizumab, and continue methylprednisolone 1 000 mg per day intravenously for 2 or more days.</td><td>• Administer dexamethasone[5] 10 mg intravenously every 6 hours.<br>• Continue dexamethasone use until resolution to Grade 1 or less, then taper.<br>• Alternatively, consider administration of methylprednisolone 1 000 mg per day intravenously for 3 days; if symptoms improve, then manage as above.</td></tr>
<tr><td colspan="2"></td><td colspan="2">Permanently discontinue Columvi.<br><br>Consider non-sedating, anti-seizure medicinal products (e.g., levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists for further evaluation, as needed. In case of raised intracranial pressure/cerebral oedema, refer to institutional guidelines for management.</td></tr>
</table>

[1] ASTCT consensus grading criteria for ICANS (Lee 2019).
[2] Management is determined by the most severe event, not attributable to any other cause.
[3] If patient is arousable and able to perform **Immune Effector Cell-Associated Encephalopathy (ICE) Assessment,** assess:
**Orientation** (oriented to year, month, city, hospital = 4 points);
**Naming** (name 3 objects, e.g., point to clock, pen, button = 3 points);
**Following commands** (e.g., “show me 2 fingers” or “close your eyes and stick out your tongue” = 1 point);
**Writing** (ability to write a standard sentence = 1 point;
**Attention** (count backwards from 100 by ten = 1 point).
**If patient is unarousable and unable to perform ICE Assessment** (Grade 4 ICANS) = 0 points.
[4] Attributable to no other cause.
[5] All references to dexamethasone administration are dexamethasone or equivalent.

4.4 Special warnings and precautions for use

Immune effector cell-associated neurotoxicity syndrome

Serious cases of immune effector cell-associated neurotoxicity syndrome (ICANS) which could be life-threatening or fatal have occurred following treatment with Columvi (see section 4.8).

The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS. Clinical signs and symptoms of ICANS may include but are not limited to confusion, depressed level of consciousness, disorientation, seizure, aphasia, and dysgraphia.

Patients should be monitored for signs and symptoms of ICANS following Columvi administration and treated promptly. Patients must be counselled to seek immediate medical attention should signs or symptoms occur at any time (see *Patient card* below).

At the first signs or symptoms of ICANS, manage according to the ICANS guidance provided in Table 4. Treatment with Columvi should be withheld or discontinued permanently as recommended.

Patient card

The prescriber must inform the patient of the risk of CRS and ICANS and the signs and symptoms of CRS and ICANS. Patients must be instructed to seek immediate medical attention if they experience signs and symptoms of CRS and ICANS. Patients should be provided with the patient card and instructed to carry the card at all times. This card describes symptoms of CRS and ICANS which, if experienced, should prompt the patient to seek immediate medical attention.

4.7 Effects on ability to drive and use machines

Columvi has ~~minor~~ major influence on the ability to drive and use machines.
Due to the potential for ICANS patients receiving Columvi are at risk of depressed level of consciousness (see section 4.4). Patients ~~experiencing symptoms~~ should be instructed to avoid driving or operating machines for 48 hours after each of the first two doses during the step-up phase and in the event of new onset of any symptoms of ICANS (confusion, disorientation, depressed level of consciousness) and/or CRS (pyrexia, tachycardia, hypotension, chills, hypoxia), ~~should be advised not to drive or use machines,~~ until symptoms resolve (see sections 4.4 and 4.8).

4.8 Undesirable effects

Tabulated list of adverse reactions

| **System organ class** | **Adverse reaction** | **All grades** | **Grade 3-4** |
|---|---|---|---|
| **Nervous system disorders** | Immune effector cell-associated neurotoxicity syndrome[13] | Common | Uncommon |

[13] ICANS based on Lee 2019 and includes somnolence, cognitive disorder, confusional state, delirium, and disorientation.

Description of selected adverse reactions

*Immune effector cell-associated neurotoxicity syndrome*
ICANS, including Grade 3 and higher, were reported in clinical trials and with post-marketing experience. The most frequent clinical manifestations of ICANS were confusion, depressed level of consciousness, disorientation, seizure, aphasia, and dysgraphia. Based on the available data, the onset of neurologic toxicity was concurrent with CRS in majority of cases.

The observed time to onset of the majority of ICANS was 1-7 days with median of 2 days after the most recent dose. Only few events were reported to have occurred more than one month after the initiation of Columvi.

**Package leaflet**

2. What you need to know before you are given Columvi

[...]

**Tell your doctor straight away** if you experience any of the following side effects while receiving Columvi. The symptoms of each side effect are listed in section 4.

[...]

• **Neurologic toxicity including immune effector cell-associated neurotoxicity syndrome:** Effects on the nervous system. Symptoms include feeling confused, disoriented, feeling less alert, having seizure or having difficulty writing and/or speaking. Close monitoring is needed.

[…]

**Driving and using machines**

Columvi ~~has minor~~ may influence ~~on~~ your ability to drive, cycle or use any tools or machines.

~~If you feel any symptoms that may affect your ability to drive, including symptoms of cytokine release syndrome (such as fever, fast heartbeat, feeling dizzy or lightheaded, chills or shortness of breath) – do not drive, cycle or use any tools or machines until you feel better.~~

Do not drive, use tools, or operate machines for at least 48 hours after each of your first two doses of Columvi or if you develop symptoms of ICANS (such as feeling confused, disoriented, feeling less alert, having seizure or having difficulty writing and/or speaking) and /or symptoms of cytokine release syndrome (such as fever, fast heartbeat, feeling dizzy or lightheaded, chills or shortness of breath). If you currently have such symptoms, avoid these activities and contact your doctor, nurse, or pharmacist. See section 4 for more information about side effects.

4. Possible side effects

Serious side effects

**Tell your doctor straight away** if you get any of the serious side effects listed below – you may need urgent medical treatment.

[...]

• **Immune effector cell-associated neurotoxicity syndrome (common):** symptoms may include, but are not limited to, confusion, disorientation, feeling less alert, seizures, or having difficulty writing and/or speaking

## ANNEX II D CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

**Additional risk minimisation measures: Patient card**

All patients who receive Columvi shall be provided with a patient card, which will contain the following key elements:

- Contact details of the Columvi prescriber.
- List of CRS and ICANS symptoms to prompt patient actions including to seek immediate medical attention in case of their occurrence.
- Instructions that the patient should carry the patient card at all times and to share it with HCPs involved in their care (i.e., urgent care HCPs, etc.).
- Information for the HCPs treating the patient that Columvi treatment is associated with the risk of CRS and ICANS.

# 4. Glucagon-like peptide-1 (GLP-1) receptor agonists: dulaglutide; exenatide; insulin degludec, liraglutide; liraglutide; insulin glargine, lixisenatide; lixisenatide; semaglutide; tirzepatide – Aspiration and pneumonia aspiration (EPITT no 19974)

**Summary of product characteristics**

4.4 Special warnings and precautions for use

*Substances: semaglutide, liraglutide, insulin degludec/liraglutide, dulaglutide, lixisenatide, insulin glargine/lixisenatide, exenatide*

Aspiration in association with general anaesthesia or deep sedation

Cases of pulmonary aspiration have been reported in patients receiving GLP-1 receptor agonists undergoing general anaesthesia or deep sedation. Therefore, the increased risk of residual gastric content due to delayed gastric emptying (see section 4.8) should be considered prior to performing procedures with general anaesthesia or deep sedation.

*Substance: tirzepatide*

Aspiration in association with general anaesthesia or deep sedation

Cases of pulmonary aspiration have been reported in patients receiving GLP-1 receptor agonists undergoing general anaesthesia or deep sedation. Therefore, the increased risk of residual gastric content due to delayed gastric emptying (see section 5.1) should be considered prior to performing procedures with general anaesthesia or deep sedation.

**Package leaflet**

*Substances: semaglutide, liraglutide, insulin degludec/liraglutide, dulaglutide, lixisenatide, insulin glargine/lixisenatide, exenatide, tirzepatide*

2. What you need to know before you use [product name]

Warnings and precautions

If you know that you are due to have surgery where you will be under anesthesia (sleeping), please tell your doctor that you are taking [product name].

# 5. Human papillomavirus 9-valent vaccine (recombinant, adsorbed); human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed) – Granuloma (EPITT no 20046)

**Summary of product characteristics**

4.8 Undesirable effects

General disorders and administration site conditions

Frequency "Uncommon": Injection site nodule

**Package leaflet**

4. Possible side effects

Frequency "Uncommon (may affect up to 1 in 100 people)": lump (nodule) at the injection site