Bundesamt für Sicherheit
im Gesundheitswesen

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Ihr Zeichen:

Betreff: Budesonid – hältige Arzneispezialitäten – Änderungen der Fach- und Gebrauchsinformationen aufgrund des HBD – PSUR Worksharing Projektes

Sehr geehrte Damen und Herren,

basierend auf der Evaluierung des PSURs im EU-HBD-worksharing Projekt (Verfahrensnummer: DK/H/PSUR/0041/002) kommt es zu der Empfehlung, folgende Ergänzungen in die **Fach- und Gebrauchsinformation** aller Budesonid – hältigen Arzneispezialitäten zur aufzunehmen.

Sollten diese bereits aufgenommen worden sein, betrachten Sie dieses Schreiben als gegenstandslos.

RECOMMENDED CHANGES TO THE PRODUCT INFORMATION

The following changes to the product information of medicinal products containing the active substance budesonide are recommended:

Summary of product characteristics

The following amendments or additions should be made to the SmPCs of all brands. Text in brackets is not part of this assessment and is only used in the example to show its position in SmPCs where it already exists. Slashes show alternatives; for each SmPC the most appropriate should be chosen.

All forms, section 4.5: Addition of the text "Because adrenal function may be suppressed, an ACTH stimulation test for diagnosing pituitary insufficiency might show false results (low values)"

Inhaled forms, section 4.6:
The following should be added, and possible contradictory text removed:

"Most results from prospective epidemiological studies and world-wide post-marketing data have not been able to detect an increased risk for adverse effects for the fetus and newborn child from the use of inhaled budesonide during pregnancy. [The risk.... considered.] It is important for both foetus and mother to maintain an adequate asthma treatment during pregnancy. As with other drugs administered during pregnancy, the benefit of the administration of budesonide for the mother should be weighed against the risks to the foetus."

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Inhaled forms, section 4.8

The frequency of cataract in SmPC section 4.8 should be amended to "uncommon", based on the guidance given in the SmPC guideline.

A statement can be accepted, noting that in placebo-controlled studies, cataract was also uncommonly reported in the placebo group. The text should be situated in a subsection c: "description of selected adverse events" as advised in the SmPC guideline.

The ADR "muscle spasm" should be added to section 4.8 with the frequency "uncommon".

The ADR "tremor" should be added to section 4.8 with the frequency "uncommon" based on the frequency of 0.27% reported in clinical trials.

MAHs should ensure that inhaled budesonide SmPCs contain in section 4.8 outside the table a general statement on the possibility of systemic ADRs. The statement should include the following text or similar:

"Occasionally, signs or symptoms of systemic glucocorticosteroid-side effects may occur with inhaled glucocorticosteroids, probably depending on dose, exposure time, concomitant and previous corticosteroid exposure, and individual sensitivity."

The frequencies of anxiety and depression should be amended to "uncommon".

The following text may be included in a footnote or preferably subsection c) of section 4.8 (in accordance with SmPC guidance). The term "inhaled budesonide" or similar may be employed for generic products:

"Clinical trials with 13119 patients on Pulmicort(/inhaled budesonide) and 7278 patients on placebo have been pooled. The frequency of anxiety was 0.52% on Pulmicort(/inhaled budesonide) and 0.63% on placebo; that of depression was 0.67% on Pulmicort and 1.15% on placebo."

Inhaled forms with indication COPD, section 4.4 and 4.8:

Include text on pneumonia in section 4.4, which replaces current text on the topic in section 4.8:

"Clinical studies and meta-analyses indicate that treatment of COPD with inhaled corticosteroids may lead to an increased risk of pneumonia, including severe pneumonia. The absolute risk for budesonide is small. In a meta-analysis of 8 COPD double blind trials, pneumonia occurred in 3.1% of 4215 patients on budesonide and in 2.8% of 2796 patients on placebo. Pneumonia serious adverse events occurred in 1.4% of 3948 patients on budesonide and 0.9% of 2524 patients on placebo. ~~I~~n the individual patient frequently experiencing pneumonias, the treatment should be reconsidered."

In addition, the ADR pneumonia should be added to section 4.8 with the frequency "common". A statement can be accepted, noting that in placebo-controlled studies, pneumonia was also commonly reported in the placebo group. The text should be situated in a subsection "description of selected adverse events", cross-referring to section 4.4 in line with the SmPC guideline. Contradictory text to the statement in 4.4, should be removed or amended.

Intranasal forms, section 4.8:

The ADR "muscle spasm" should be added to section 4.8 with the frequency "uncommon".

The ADRs Nasal ulcer, Nasal septum perforation, Anaphylactic reaction, Dysphonia should be given the frequency "rare".

MAHs should ensure that intranasal budesonide SmPCs contain in section 4.8 outside the table a general statement on the possibility of systemic ADRs. The statement should include the following text or similar:

"In rare cases, signs or symptoms of systemic glucocorticosteroid-side effects may occur with nasal glucocorticosteroids, probably depending on dose, exposure time, concomitant and previous corticosteroid exposure, and individual sensitivity."

Based on mechanistic plausibility and extrapolation from other budesonide/corticosteroid formulations, the ADR "contusion" should be added to the ADR table. The frequency should be "rare".

Enteral forms, section 4.8

The psychiatric terms "anxiety", "depression", "psychomotor hyperactivity" and "aggression" should be added to the ADR table. The frequency should be "common" for depression, "uncommon" for psychomotor hyperactivity and anxiety, and "rare" for aggression.

The ADR "cataract including subcapsular cataract" should be added to the SmPCs of enteral forms, with a frequency of "rare".

Based on mechanistic plausibility and extrapolation from other budesonide/corticosteroid formulations, the ADR "ecchymosis" should be added to the SmPC. The frequency should be "rare".

In SmPCs where the ADRs in the table below are mentioned, their frequencies should be stated as below:

ADR	**Frequency**
Dyspepsia	Common
Glaucoma	Rare
duodenal or gastric ulcer	Uncommon
pancreatitis	Rare
osteonecrosis	rare
anxiety	Uncommon
depression	Common
Psychomotor hyperactivity	Uncommon
aggression	Rare
Ecchymosis	Rare
Cataract	Rare

The following statement should be included in a section c) below the ADR table:

"Most of the adverse events mentioned in this SmPC can also be expected for other treatments with glucocorticoids."

Enteral forms authorised by Dr. Falk, section 4.8

For those products, the ADRs should be listed in a table based on the SmPC approved in procedure UK/H/2778/001/II/004 (capsules form) with amendments recommended in this PSUR. For rectal forms, ADRs due to the different local use should be added to the table which is given below:

System organ class	Frequency according to MedDRA convention	Reaction
Metabolism and nutrition disorders	Common	Cushing's syndrome: e.g. with moon face, truncal obesity, reduced glucose tolerance, diabetes mellitus, hypertension, sodium retention with oedema, increased potassium excretion, inactivity or atrophy of the adrenal cortex, red striae, steroid acne, disturbance of sex hormone secretion (e.g. amenorrhoea, hirsutism, impotence)
	Very rare	Growth retardation in children
Eye disorders	Rare	Glaucoma, cataract
Gastrointestinal disorders	**Common**	**Dyspepsia**
	Uncommon	**Duodenal or gastric ulcer**
	Rare	**Pancreatitis**
	Very rare	Constipation
Immune system disorders	Common	Increased risk of infection
Musculoskeletal and connective tissue disorders	Common	Muscle and joint pain, muscle weakness and twitching, osteoporosis
	Rare	**Osteonecrosis**
	~~Very rare~~	~~Aseptic necrosis of bone (femur and head of the humerus)~~
Nervous system disorders	Common	Headache
	Very rare	Pseudotumor cerebri including papilloedema in adolescents
Psychiatric disorders	Common	Depression, irritability, euphoria
	Uncommon	**Psychomotor hyperactivity anxiety**
	Rare	**Aggression**

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System organ class	**Frequency according to MedDRA convention**	**Reaction**
	~~Very rare~~	~~Manifold psychiatric effects or such as impair behaviour~~
Skin and subcutaneous tissue disorders	Common	Allergic exanthema, petechiae, delayed wound healing, contact dermatitis.
	Rare	**Ecchymosis**
Vascular disorders	Very rare	Increased risk of thrombosis, vasculitis (withdrawal syndrome after long-term therapy).
General disorders	Very rare	Fatigue, malaise

The package leaflet should be updated accordingly.

Oben angeführte Textabschnitte stellen eine Mindestanforderung dar, zusätzliche nationale Hinweise in diesen Abschnitten sind zu belassen.