Well-Established Use Applications

REFLECTION OF THE REALITY

MARINA FERTEK

PRAGUE, SEPTEMBER 2019

Well-Established Use Applications

Reasons for failure/difficulties of WEU applications

- Insufficient research of the WEU qualifiers by the companies
- Attempt to circumvent the generic application
- Possible formulation effect
- No official guidelines on the requirements for WEU products
- Variable quality of the PARs
- Non-harmonized and unpredictable assessment by the regulatory agencies

Challenges of the WEU applications

- Justification of the WEU – often only „10 years“ criterion addressed, but others are forgotten
- Appropriateness of the literature references – date of publications, quality of the literature in relation to the proposed indication and posology, patient population
- Consistency of the regulatory assessment – different conclusions for the same evidence
- The need for the PK bridging study of the to-be-marketed product to the literature

Evidence supporting the efficacy and safety

- Date of publications: old molecule = old studies
- Assessors sometime reject these old studies: „*The requirements on efficacy and safety change over time and new products need to follow the current ones. The studies provided contained multiple flaws, were not consistent or robust*“.
- Positive benefit/risk, confirmed by clinical practice and therapeutic guidelines is disregarded in this case. This is is in contrast with the principles of the well-established use where interest of the medical community (i.e. therapeutic guidelines) should be taken into account as one criterion of the well-established use.

Curious case of vitamin D

- The well-established use indication of vitamin D is „treatment of the vitamin D deficiency“
- WEU criteria are fulfilled: presence on the EU market in doses up to 100 000 IU, all have PV measures in place, used in medical practice
- Scientific literature is based on randomized clinical trials, metaanalyses and reviews, therapeutic guidelines on the treatment of the vitamin D deficiency
- Treatment is individual and dose adjusted according to the biochemical marker – i.e. posology is up to the prescribing physician

Currently approved vitamin D -containing products

procedure	Therapeutic indications	Posology
DK/H/2491/001-003/DC, Benferol 25,000 IU/Soft capsules 50,000 IU/Soft capsules 100,000 IU/Soft capsules	Prophylaxis and treatment of vitamin D deficiency in adults and adolescents (children ≥ 12 years). Vitamin D deficiency is defined as serum levels of 25-hydroxycolecalciferol (25(OH)D) <25 nmol/l. In addition to specific therapy for osteoporosis in patients with vitamin D deficiency or at risk of vitamin D insufficiency, preferably in combination with calcium.	Recommended dose: One capsule 25,000 IU/month Treatment of vitamin D deficiency: The dose should be adjusted dependent upon desirable serum levels of 25-hydroxycolecalciferol (25(OH)D), the severity of the disease and the patient's response to treatment. Treatment of symptomatic vitamin D deficiency: 100,000 IU loading dose or equivalent (2 x 50,000 IU in 1 week). A maintenance dose of 25,000 IU/month should be considered one month after loading dose.
ES/H/0386/001-003/DC D-FORCE/D-FORCE FORTE 25.000 UI/oral solution 50.000 UI/oral solution 100.000 UI/oral solution	Treatment of vitamin D deficiency in adults and adolescents (children ≥12 years). Vitamin D deficiency is defined as serum levels of 25-hydroxycholecalciferol (25 (OH) D) <25 nmol/l.	Adults and adolescents (children ≥ 12 years old) Recommended dose: - Prevention of vitamin D deficiency and as a coadjuvant to a specific treatment of osteoporosis: a vial of 25,000 IU / month - Treatment of vitamin D deficiency: the dose should be adjusted according to the desirable serum levels of 25-hydroxycholecalciferol (25 (OH) D), the severity of the disease and the patient's response to treatment. - Treatment of symptomatic vitamin D deficiency: loading dose of 100,000 IU or equivalent (2 doses of 50,000 IU in 1 week). A maintenance dose of 25,000 IU / month should be considered one month after the loading dose.
NL/H/3391/001/DC, invita D3/ Benferol 800 IU/soft gel capsules	Prophylaxis and treatment of vitamin D deficiency in adults and adolescents with an identified risk. In addition to specific osteoporosis treatment of patients who are at risk of vitamin D deficiency, preferably in combination with calcium.	Recommended dose: One capsule per day. Higher doses can be necessary in treatment of vitamin D deficiency, where the dose should be adjusted dependent upon desirable serum levels of 25-hydroxycolecalciferol (25(OH)D), the severity of the disease and the patient´s response to treatment. The daily dose should not exceed 4,000 IU (5 capsules per day).
NL/H/3449/001/DC, Benferol 5600 IE/soft capsules	Prophylaxis and treatment of vitamin D deficiency in adults and adolescents with an identified risk. In addition to specific osteoporosis treatment of patients who are at risk of vitamin D deficiency, preferably in combination with calcium.	Recommended dose: One capsule per week. Higher doses can be necessary to achieve desirable serum levels of 25-hydroxycolecalciferol (25(OH)D). The weekly dose should not exceed 5 capsules.
SE/H/1122/001/DC, Desunin/ Divisun 800 IU/tablet	Prevention and treatment of vitamin D deficiency in adults and adolescents. In addition to specific osteoporosis treatment of patients who are at risk of vitamin D deficiency, supplemental calcium should be considered.	Recommended dose: One tablet per day. Higher dosed can be necessary to achieve desirable serum levels of 25-hydroxycolecalciferol (25(OH)D). The daily dose should not exceed 5 tablets.

Comments from different authorities on the new application of high-dose vitamin D

- RMS comment: *Insufficient evidence of efficacy and safety of the large dose (100 000 IU) formulation of vitamin. They wanted indications and posology to be supported from the published literature. 50 000 IU is approvable.*
- CMS comment: *100,000 IU is considered approvable for the treatment of vitamin D deficiency in high risk patients, when monitoring serum 25(OH)D and calcium after the initial dose. This is in line with earlier approved 100,000 IU vitamin D products. 50 000 IU not approvable as it exceeds the maximum recommended dose (safety concern)*
- *CMS comment: did not prefer the general D-vitamin deficiency risk factor check list in the posology section. The indication is: "Initial treatment of clinically relevant vitamin D deficiency in adults." The need of initial high dose vitamin D treatment should be determined based on severity of the deficiency*

Comments from different authorities on the new application of high-dose vitamin D

- CMS comment: *a well-established use has to be denied both for both strengths. Adequate confirmatory studies must be available to show an effective and safe treatment in long-term use for such high dosages. This means, it is not sufficient to show that the dosage is safe, only. In addition, a proven efficacy and a therapeutic use for at least ten years of such a dose regimen in the indications claimed have to be shown, too. These data, however, have not been provided by the applicant.*
- CMS comment: *does not endorse the "Cumbria Guidelines" that allow doses up to 50,000 IU once per week for a duration of 6 weeks and a loading dose of 300,000 IU in total.*

- Indications approved across EU vary from prophylaxis, treatment of Vitamin D deficiency, osteoporosis
- Several agencies have denied applications based on risk of high doses and also have approved them
- The same data-set is available to all Applicants for WEU application of Vitamin D which was informally confirmed
- Older approvals of Vitamin D remain with elaborated indications, whereas more recent approvals have much further restrictions of indications
- Applicant do not want to be the scapegoat of referrals to attempt to align EU-wide attitude to WEU of Vitamin D

The problem of the PK bridging study

- Often the request to bridge the to-be-marketed product to the available literature is made by the Agencies
- The question is: What is the other end of the bridge??
- The drug used in the published trials is often cited as INN, not possible to identify the manufacturer
- Not possible to obtain details on the formulation
- No product currently available on the EU market

Bridging study – dexamethasone case

- Dexamethasone Oral Solution, Alapis SA (EMEA/H/A-29/1308)
- Majority of the literature was with tablets
- CMS considered that the literature data on Dexamethasone tablets that had been submitted could not be extrapolated to Dexamethasone oral solution without adequate bridging data.
- CHMP referral in 2011
- The Company applied for a BCS biowaiver
- The Company provided data that showed that irrespective of the immediate- release oral dosage formulation (tablet or solution), the bioavailability of Dexamethasone, in terms of extent and rate of absorption, was similar.
- 1) a parallel artificial membrane permeability assay (PAMPA) data study,
- 2) literature, and
- 3) dissolution data.

- CHMP concluded on a positive benefit/risk balance for the product.

Bridging study – glycopyrronium bromide case

- Sialanar (EMEA/H/C003883/0000) was a PUMA procedure that was approved in 2016 as WEU, but only after reexamination
- Indication was sialorrhea in children with neurological disorder
- Except for UK, there was no experience with glycoprronium in the EU
- Glycoprronium-containing product Cuvposa was present on the US market, but in different concentration. This product was also used in some published efficacy studies
- The Company performed comparative PK study with Cuvposa
- The study failed to meet BE criteria
- After adjusting the posology, the study was accepted

Bridging study – low-dose gastroresistant ASA

- Procedure SE/H/1020/002-005/DC
- Submitted as WEU for 75 – 160 mg strengths
- BES with 100 mg against Aspirin Protect - one in the fed state and three in the fasting state.
- Only fed study met the bioequivalence criteria
- RMS conclusion: *This is not considered a critical finding as the products are applied via a bibliographic application where the bibliographic clinical data on ASA in the applied indication consists of studies performed with several different formulations and doses. Our conclusion is that the presented studies demonstrate that the formulation is sufficiently similar to the formulations used in the bibliographic data referred to.*

Conclusions

- Case of vitamin D is an illustration of significant disharmony, not only among agencies, but also within on agency
- PARs do not contain enough information on the grounds for acceptance/refusal, thus making it increasingly difficult to predict the outcome
- Referrals are good tool to reach harmonization, but are tedious for the agencies and risky for the companies
- The request for the PK bridging study is justified in some cases, in others it essentially brings no additional value
- Clinical and quality assessor should make judgement whether products are considered similar before requesting in vivo study by default

Conclusions

- What to do with Art. 10a??

- Create WEU monographs, similarly to herbals
- Erase Art. 10a off the face of the Earth ☺

Thank you for your attention

Acknowledgements:

Dr Parvinder Punia, Pharmexon Consulting, Prague

Dr Anjana Aggarwal, independent consultant