

## 1.1. Vitamin B12 and acneiform dermatitis

### Introduction

Vitamin B12 preparations are indicated *for prophylaxis and as therapy for vitamin B12 deficiency caused by megaloblastic (pernicious) anaemia, which can be accompanied by neurological diseases* [1]. Preparations of vitamin B12 for therapeutic use contain either hydroxocobalamin or cyanocobalamin. Hydroxocobalamin (Hydrocobamine<sup>®</sup> [1], Hydroxocobalamine<sup>®</sup> [2] and Cyanokit<sup>®</sup>) [3] was registered in 1966. Cyanocobalamin (Soluvit N<sup>®</sup> [4], Cernevit<sup>®</sup> [5] and Cyanocobalamine<sup>®</sup> [6]) was registered in 1982.

Acne Vulgaris is a self-limited skin disorder usually localized on the face, but also on the upper part of the chest and back, where the skin is rich in sebaceous glands. It commonly occurs in puberty and adolescence. It is characterized by comedones, papules, nodules, and cysts due to obstruction and inflammation of pilosebaceous units. The pathogenesis involves the overproduction of sebum (seborrhoe) and follicular epidermal hyperproliferation resulting in obstruction of the follicle with sebum and desquamated keratinocytes. Infection with the normal skin anaerobe *Propionibacterium acnes* may stimulate inflammation in the follicle; acne can be noninflammatory or inflammatory [7,8].

Up to 2005, Lareb received 5 reports of acneiform dermatitis after intramuscular vitamin B12 supplementation. This resulted in a quarterly report in the fourth quarter of 2005 [9]. In 2008, Lareb published an article about acneiform dermatitis concerning 10 patients with the use of vitamin B12 [10]. Up to 2010, Lareb has received a total of 35 reports of vitamin B12 associated with acne or acneiform dermatitis. The SmPC of Cyanokit<sup>®</sup> reports pustular rash, mainly in the face and neck. Also a reversible redness of the skin and mucous membranes is mentioned. The described ADR might correspondent with acneiform dermatitis. The association of acneiform dermatitis and vitamin B12 has not yet been described in any of the other SmPCs.

### Reports

Up to November 1<sup>st</sup>, 2010, Lareb received a total of 35 reports with acne or acneiform dermatitis with the use of vitamin B12. These reports concerned eight reports where vitamin B12 was associated with the occurrence of acneiform dermatitis, 3 reports of acneiform rash with vitamin B12 and also another 24 reports where vitamin B12 was associated with the occurrence of acne. Nineteen of these 35 reports in total were reported by consumers. The other 16 reports were received from health professionals. Four of them were reported by a dermatologist (patients H, CC, GG and HH) and one report was reported by an allergist (patient B).

In most reports hydroxocobalamin was used. Three of the 35 reports concerned acne or acneiform dermatitis with the use of cyanocobalamin. Patients GG, HH, and II used a combination of thiamine, pyridoxine and cyanocobalamin. There is no SmPC available anymore for this drug, but because these products also contain cyanocobalamin, they were included in Table 1.

All reports, except for four patients, concerned women. Nearly all patients were of premenopausal age. Two patients (I and D) were younger than 16 years old. Report B was reported by an allergist. Reports CC, GG and HH were reported by a dermatologist. Most of the reports were reported by pharmacist or consumers and the term 'acne' was mentioned in the original text. The corresponding MedDRA term 'acne' was used for coding of these reports, see Table 1.

Latency time varied between one day to two months. Patients Q, J and FF mentioned that they suffered from acne after every injection. Patient J also mentioned a duration of the reaction of one week. Patient A also had symptoms when using vitamin B12 four years before.

Several patients were treated for their acne or acneiform dermatitis with contraceptives (patients V and GG were treated with cyproterone/ ethinylestradiol), topical application of erythromycin, benzoylperoxide, cortisone ointment, ceterizine or doxycycline. Patient E and T also had acne before the start of vitamin B12 injections.

Table 1. Reports of acne or acneiform dermatitis associated with the use of vitamin B12

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 46551 F, 31 – 40 years	hydroxocobalamin 1mg once monthly anaemia vitamin B12 deficiency	metronidazole, vitamin d	acneiform dermatitis	13 days no change unknown
B 49130 F, 21 – 30 years	cyanocobalamin 1mg once weekly fatigue	montelukast, levoceterizine, fluticasone nasal spray atenolol, levothyroxine	acneiform dermatitis	few months unknown not recovered
C 106648 F, 31 – 40 years	cyanocobalamin 1mg unknown vitamin B12 deficiency	non-specified homeopathic drug	acneiform dermatitis	2 weeks no change not recovered
D 109551 F, 11 – 20 years	hydroxocobalamin 1mg once weekly pernicious anaemia	ethinylestradiol/ levonorgestrel	acneiform dermatitis	7 weeks dose reduction not recovered
E 108337 F, 51 – 60 years	hydroxocobalamin 1mg unknown vitamin B12 deficiency	cholecalciferol	acneiform dermatitis	1 month discontinued unknown
F 61968 M, 21 – 30 years	hydroxocobalamin 1mg once weekly anaemia		acneiform dermatitis	1 week no change not recovered
G 71756 F, 31 – 40 years	hydroxocobalamin 1mg unknown pernicious anaemia		acneiform dermatitis	few days no change not recovered
H 109360 F, 31 – 40 years	hydroxocobalamin 1mg twice weekly vitamin B12 deficiency		acneiform dermatitis	2 weeks no change not recovered
I 50313 F, 11 – 20 years	hydroxocobalamin 1mg unknown unknown	ferrous fumarate, losferon	rash acneiform	2 weeks unknown unknown
J 51802 F, 51 – 60 years	hydroxocobalamin 1mg unknown vitamin B12 deficiency	levothyroxine	rash acneiform	2 weeks after every injection, duration 1 week no change recovered
K 78610 M, 31 – 40 years	hydroxocobalamin 1mg unknown unknown	paracetamol, pramocaine/zinc oxide cream	rash acneiform	unknown unknown unknown
L 50955 M, 31 – 40 years	hydroxocobalamin 1mg once weekly vitamin B12 deficiency		acne, ear pain, headache, dizziness	10 days no change recovered with sequelae

<b>Patient, Sex, Age</b>	<b>Drug Indication for use</b>	<b>Concomitant medication</b>	<b>Suspected adverse drug reaction</b>	<b>Time to onset, Action with drug outcome</b>
M 66652 F, 51 – 60 years	hydroxocobalamin 1mg twice weekly vitamin B12 deficiency		acne	8 days unknown not recovered
N 70418 M, 31 – 40 years	hydroxocobalamin 1mg unknown vitamin B12 deficiency		acne	3 weeks no change unknown
O 73151 F, 31 – 40 years	hydroxocobalamin 1mg once every 10 days pernicious anaemia		acne, food craving, depressed mood	1 month no change not recovered
P 80845 F, 31 – 40 years	hydroxocobalamin 1mg once weekly vitamin B12 deficiency		acne	3 weeks no change recovering
Q 90388 F, 41 – 50 years	hydroxocobalamin 1 mg once weekly unknown	ethinylestradiol/ levonorgestrel	acne	after every injection no change not recovered
R 91060 F, 21 – 30 years	hydroxocobalamin 1 mg once per 2 weeks vitamin B12 deficiency	ethinylestradiol/ norgestimate, desloratadine	acne	2 months no change not recovered
S 91618 F, 31 – 40 years	hydroxocobalamin 1 mg unknown unspecified vitamin deficiency		acne like symptoms	3 weeks unkown unknown
T 92217 F, 21 – 30 years	hydroxocobalamin 1 mg unknown unknown		acne, tinea, herpes zoster	7 days no change not recovered
U 92701 F, 31 – 40 years	hydroxocobalamin 1 mg once weekly vitamin B12 deficiency		acne	10 days no change not recovered
V 92727 F, 21 – 30 years	hydroxocobalamin 1 mg once weekly vitamin B12 deficiency	cromolyn eye drops, cyproterone/ ethinylestradiol	acne	10 days no change not recovered
W 93360 F, 31 – 40 years	hydroxocobalamin 1 mg twice daily vitamin B12 deficiency		acne pustular	9 days no change not recovered
X 95555 F, 61 – 70 years	hydroxocobalamin 1 mg once weekly vitamin B12 deficiency		acne, diarrhoea	2 months no change not recovered
Y 103473 F, 31 – 40 years	hydroxocobalamin 1 mg twice weekly vitamin B12 deficiency, pernicious anaemia		acne	2 months no change not recovered
Z 104284 F, 31 – 40 years	hydroxocobalamin 1 mg twice weekly vitamin B12 deficiency		acne	1 week no change not recovered

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
AA 104294 F, 31 – 40 years	hydroxocobalamin 1 mg once per 3 days vitamin B12 deficiency		acne, rash	1 week no change recovered
BB 104462 F, 31 – 40 years	hydroxocobalamin 1 mg once weekly vitamin B12 deficiency		acne	3 weeks no change not recovered
CC 104597 F, 21 – 30 years	hydroxocobalamin 1 mg unknown unknown		acne	1 week no change not recovered
DD 110427 F, 21 – 30 years	hydroxocobalamin 1 mg once daily vitamin B12 deficiency		acne	8 days discontinued not recovered 2 days after withdrawal
EE 110780 F, 31 – 40 years	hydroxocobalamin 1 mg vitamin B12 deficiency		acne	7 days not applicable not yet recovered
FF 111022 F, 21 – 30 years	cyanocobalamin 1mg anaemia	paroxetine, levothyroxin, ferrosulphate	acne	1 day after every injection no change not yet recovered
GG* 91971 F, 41 – 50 years	thiamine, pyridoxine, cyanocobalamin 1 mg unkown vitamin B12 deficiency, iron deficiency		acne vulgaris	few weeks no change recovering
HH* 91987 F, 41 – 50 years	thiamine, pyridoxine, cyanocobalamin 1 mg unknown vitamin B12 deficiency	pantoprazole, tramadol, paracetamol/code ine	acne	1 week unknown recovering
II 98099 F, 11 – 20 years	thiamine, pyridoxine, cyanocobalamin 1 mg once per 4 weeks vitamin B12 deficiency, crohn's disease  thioguanine 40mg once per 2 days 20 mg		acne	9 days withdrawn recovered with sequelae

\* Patients GG and HH are reported by the same reporter.

## Other sources of information

### Literature

Braun-Falco *et al.* [11], described deterioration of acne vulgaris or eruption of acneiform exanthema during treatment with vitamin B6 and/ or vitamin B12 in fourteen patients. The symptoms consisted of small papules or papulopustules on the face, upper parts of the back and chest. After withdrawal of vitamin B6 or vitamin B12, the acneiform rash disappeared within a short time interval.

Another case report was described by Sherertz [12]. The patient suffered from an eruption resembling acne rosacea which was associated with the daily use of a high-dose vitamin B supplement. The acne did not respond to the usual treatment for acne rosecea. A positive dechallenge was found.

In the article by Jansen *et al.* [13], rosacea fulminans with sudden onset was described with the use of high-dose vitamins B6 and B12 in a 17-year old girl. The eruption improved when the vitamins were withdrawn and treatment with isotretinoin and methylprednisolone was started. Jansen *et al.*, concluded that it seems appropriate to consider new or exacerbating facial eruptions due to the use of vitamin B.

### Databases

On November 24 2010, the association between acne or acneiform dermatitis in association with the use of vitamin B12 was disproportionally present in the Lareb database and also disproportionally present in the database of the WHO.

Table 2. Reports of acnes associated with the use of vitamin B12 in the Lareb database

Drug	Number of reports	ROR (95% CI)
hydroxocobalamin	29	195.9 (123.9 - 309.6)
cyanocobalamin	3	232.8 (55.3 - 979.3)
vitamin B1 and B6 and/or vitamin B12	3	317.3 (75.3 - 1337.4)

For the Lareb database the High Level Term acnes was taken into account. This term includes all the Lower Level Terms as reported in Table 1.

Table 3. Reports of acne associated with the use of vitamin B12 in the WHO database

Drug	PT name	Number of reports	ROR (95% CI)
hydroxocobalamin	Acne	35	37.7 (26.8- 53.1)
	Dermatitis acneiform	14	133.2 (78.2-227.1)
cyanocobalamin	Acne	19	14.2 (9.0-22.3)
	Dermatitis acneiform	9	66.5 (31.3-117.1)

On December 2<sup>nd</sup> 2010, the Eudravigilance database contained four serious reports (CIOMS category of seriousness was “other”) of the Preferred Terms “acne” and “dermatitis acneiform” in association with the use of cobalamin.

### Prescription data

The number of patients using Vitamin B12 in the Netherlands is shown in table 4.

Table 4. Number of patients using Vitamin B12 in the Netherlands between 2006 and 2009 [14]

Drug	2006	2007	2008	2009
cyanocobalamin	1,841	1,654	1,773	1,605
hydroxocobalamin	98,660	102,990	112,910	126,370

### *Mechanism*

The mechanism responsible for acneiform dermatitis induced by vitamin B12 is still unknown [11]. Jansen *et al* suggest the involvement of immunological, hormonal and vascular factors. It is probable that prolonged and increased excretion of the causative substances may cause an irritation of the follicular epithelium and subsequently produce an inflammatory reaction [13].

### **Discussion**

Acne is most commonly caused by puberty, when increases in androgen leads to hyperproliferation of keratinocytes and increased sebum production. Other potential triggers are hormonal changes during the menstrual cycle and pregnancy. Two cases involved adolescents (ages 15, and 16) where hormonal changes could also have played a role in the etiology. In one patient dechallenge of vitamin B12 lead to recovery with sequelae. However, this patient was also treated with a contraceptive.

There are a few articles describing this association, the most recent one dating from 2001 [11-13]. These articles also suggest a possible relationship between the use of vitamin B12 and the occurrence of acne or acneiform dermatitis. Jansen *et al.* [13] suggest a possible mechanism for the vitamin B12 triggering acneiform dermatitis. In these articles, relatively high doses vitamin B12 were used [11-13]. No high dosages of vitamin B12 were used in the reports Lareb received.

The association between vitamin B12 and acneiform dermatitis is further supported by the disproportional high percentage in both the Lareb and WHO database suggesting a causal relationship.

### **Conclusion**

Up to 2005 Lareb received 5 reports of acneiform dermatitis after intramuscular vitamin B12 suppletion which resulted in a quarterly report. On November first, 2010, Lareb received a total of 35 reports of acne or acneiform dermatitis with the use of hydroxocobalamin or cyanocobalamin. Acne and acneiform dermatitis are still not described in the SmPC's of vitamin B12 containing products.

Acne and acneiform dermatitis should be mentioned in the SmPC's of all vitamin B12 containing products.

- Acne and acneiform dermatitis should be mentioned in the SmPC's of all vitamin B12 containing products

### References

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This signal has been raised on April 2011. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB [www.cbgmeb.nl/cbg/en/default.htm](http://www.cbgmeb.nl/cbg/en/default.htm) or the responsible marketing authorization holder(s).