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Committee on Herbal Medicinal Products (HMPC)

Addendum to Assessment report on *Cola nitida* (Vent.) Schott et Endl. and its varieties and *Cola acuminata* (P. Beauv.) Schott et Endl., semen

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HMPC decision on review of monograph *Cola nitida* (Vent.) Schott et Endl. and its varieties and *Cola acuminata* (P. Beauv.) Schott et Endl. adopted on 22 November 2011	15 January 2020
Call for scientific data (start and end date)	From 01/02/2020 to 30/04/2020
Adoption by Committee on Herbal Medicinal Products (HMPC)	05 May 2021

Review of new data on *Cola nitida* (Vent.) Schott et Endl. and its varieties and *Cola acuminata* (P. Beauv.) Schott et Endl., semen

Periodic review (from 2010 to 2020)

Scientific data (e.g. non-clinical and clinical safety data, clinical efficacy data)

- ☒ Pharmacovigilance data (e.g. data from EudraVigilance, VigiBase, national databases)
- ☒ Scientific/Medical/Toxicological databases (Web of Knowledge, PubMed, SciFinder)
- ☐ Other

Regulatory practice

- ☒ Old market overview in AR (i.e. products fulfilling 30/15 years on the market)

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☒ New market overview (including pharmacovigilance actions taken in member states)

☐ Referral

☒ Ph. Eur. monograph

☐ Other

Consistency (e.g. scientific decisions taken by HMPC)

☐ Public statements or other decisions taken by HMPC

☐ Consistency with other monographs within the therapeutic area

☐ Other

Availability of new information (i.e. likely to lead to a relevant change of the monograph)

Scientific data	Yes	No
New non-clinical safety data likely to lead to a relevant change of the monograph	☐	☒
New clinical safety data likely to lead to a relevant change of the monograph	☐	☒
New data introducing a possibility of a new list entry	☐	☒
New clinical data regarding the paediatric population or the use during pregnancy and lactation likely to lead to a relevant change of the monograph	☐	☒
New clinical studies introducing a possibility for new WEU indication/preparation	☐	☒
Other scientific data likely to lead to a relevant change of the monograph	☐	☒
Regulatory practice	Yes	No
New herbal substances/preparations with 30/15 years of TU	☐	☒
New herbal substances/preparations with 10 years of WEU	☐	☒
Other regulatory practices likely to lead to a relevant change of the monograph	☐	☒
Referrals likely to lead to a relevant change of the monograph	☐	☒
New / Updated Ph. Eur. monograph likely to lead to a relevant change of the monograph	☐	☒
Consistency	Yes	No
New or revised public statements or other HMPC decisions likely to lead to a relevant change of the monograph	☐	☒
Relevant inconsistencies with other monographs within the therapeutic area that require a change of the monograph	☐	☒
Other relevant inconsistencies that require a change of the monograph	☐	☒

Summary and conclusions on the review

During the review 164 new references not yet available during the first/previous assessment were identified.

0 references were provided by Interested Parties during the Call for data.

17 references were considered to be relevant for the assessment.

0 references justify a revision of the monograph.

No revision is considered required because neither the references published since the previous assessment nor other data (e.g. pharmacovigilance data, data from the market overview) justify the revision of the monograph.

No data were submitted during the call for scientific data period.

According to the feedback from 14 countries (Austria, Belgium, Croatia, Czech Republic, Denmark, Germany, Greece, Hungary, Ireland, Netherlands, Portugal, Spain, Slovakia, Sweden), there are no medicinal products on the market containing *Cola nitida* (Vent.) Schott et Endl. and its varieties and *Cola acuminata* (P. Beauv.) Schott et Endl., semen. In Latvia, *Cola* seed is available in one multicomponent medicinal product which does not fall into the scope of the review.

The literature search in 3 major scientific databases (PubMed, SciFinder and Web of Knowledge) resulted in 164 references in the period 2010-2020 for the search terms »*Cola nitida*« or »*Cola acuminata*«. During literature search, no filter was used for the language of publication etc. The original set of references was then analysed for articles containing data that may justify the revision of the assessment report or the monograph. 17 references contained relevant data, the majority of these reported antidiabetic (Erukainure *et al*., 2019b *in vivo*, 2017 *ex vivo*, *in vitro*, *in silico*; Oboh *et al*., 2014b *in vitro*) and central nervous system (Bisong *et al*., 2019; effect on anxiety on rats, Ishola *et al*., 2018 - *in vivo* against cognitive dysfunction) activities. A bile secretion effect of *Cola* seed was observed in an animal experiment (Nku *et al*., 2014).

Effect on the reproductive system

In an experiment, rats were treated orally with 2, 6 and 10 mg/kg *Cola* seed water extracts once daily (DER not known) for 6 weeks. Serum concentrations of luteinizing hormone (LH) and testosterone were significantly ($p<0.05$) reduced in animals treated with 6 or 10 mg/kg extracts. Sperm count was significantly lower in the treated groups ($p<0.05$) and this effect was dose-dependent. There was no change in testicular and epididymis weights (Umoh *et al*., 2014).

In an experiment, 8 mg/kg crude or decaffeinated extracts of Cola obtained with 70% methanol (DER 8.55:1) were administered to rats for 6 weeks. The crude extract resulted in no significant change in the body weight and sperm count when compared with the control group. No significant difference in seminal parameters (motility, morphology, viability), organ weight (testis) and hormonal assay (testosterone, follicle stimulating hormone, luteinizing hormone). The decaffeinated extract resulted in no change in body weight, testosterone and follicle stimulating hormone levels, seminal parameters, organ weights;

however significant increase was observed in luteinizing hormone level compared to the control group and an increase in the sperm count was also observed (p=0.02) (Ogundipe *et al*., 2016).

In a further experiment, where 8mg/kg water extract (DER not known) was applied for 4 weeks to rats, the plasma level of testosterone was significantly increased ($p<0.05$) while that of luteinizing hormone was significantly decreased ($p<0.05$) when compared with control animals (Adisa *et al*., 2010).

The administration of 25-100 mg/kg water extract of *Cola* seeds (DER 17.85:1) daily for 60 days to rats reduced the serum testosterone concentration ($p<0.05$), sperm motility and count ($p<0.0001$; $p<0.01$) compared to control animals. In addition, sperm morphology was altered; the proportion of spermatozoa with normal morphology was reduced dose-dependently ($p<0.0001$) (Aprioku and Clement, 2018). In a subsequent experiment a water extract of the seeds (DER 19.6:1) in doses of 100 and 200 mg/kg (for 30 days) decreased the sperm count ($p<0.0001$), reduced the proportion of actively motile sperms ($p<0.0001$) and increased immotile sperm proportion ($p<0.0001$) compared to the control. The proportion of sperms with normal morphology was decreased ($p<0.0001$) (Aprioku and Kari, 2018).

Exposing rats to 20 and 30 mg/kg caffeine (extracted from *Cola* seeds) intraperitoneally led to a significant ($p<0.05$) reduction in both gonadal and extra-gonadal sperm reserves (Obidike *et al*., 2011).

Assessor's conclusion on reproductive toxicology studies:

A number of studies dealt with the effect of Cola seed extracts of male reproductive system and sperm quality in animals (Adisa et al., 2010; Aprioku and Clement, 2018; Aprioku and Kari, 2018; Obidike et al., 2011; Ogundipe et al., 2016; Umoh et al., 2014). The administration of Cola seed extracts in doses of 6-200 mg daily/kg/bw (usually water extracts) affected different hormone levels, sperm quality and quantity. Non-clinical data on reproductive toxicity showing some effects on the endocrine system were not considered relevant for the human situation considering the dose administered.

Other toxicological experiments

Different papers published data on the acute (Emmanuel *et al*., 2016) or subacute toxicological properties of *Cola* seeds (Adeosun *et al*., 2017; Aprioku and Clement, 2018; Udebuani *et al*., 2017).

In an acute toxicity study on rats (Emmanuel *et al*., 2016), the LD_{50} value of an 80% methanol extract (DER not known) was determined to be 6320 mg/kg body weight. The administration of 500 mg/kg for 21 days increased ALT and AST concentrations significantly ($p<0.05$) compared to the control group.

The administration of a 80% methanol dry extract (DER not known) for rats for 14 days (100-600 mg/kg daily) did not influence plasma AST and ALT levels in the groups treated with the doses of 100-400 mg/kg, but decreased enzyme activities at higher doses (500-600 mg/kg) (Adeosun *et al*., 2017).

In a study, rats were fed for 30 days with different percentages of powdered *Cola nitida* seeds (5%, 10%, 20%, 30% and 0% w/w) in feed. AST and alkaline phosphatase activities decreased significantly ($p<0.05$) in the groups treated with a feed containing 10-30% *Cola* seed (Udebuani *et al*., 2017).

After the administration of 25-100 mg/kg water extract of *Cola* seeds (DER 17.85:1) daily for 60 days, body weigh change (gain) in treated animals was similar to control animals, however, significance was not assessed (Aprioku and Clement, 2018).

Assessor's comment:

Mostly the herbal preparations are not described properly in the articles. The effects of liver enzym on the plasma levels were detected at very high doses comparing to the human use and were contradictory (increased or decreased). Thus, no new safety issues could be identified from the articles about the acute, subacute and chronic toxicity studies.

There were no clinical trials on the efficacy or safety of Cola seeds. Papers reporting irrelevant data on secondary pharmacodynamics, e.g. antioxidant, antimicrobial activities were not considered.

There was no report on the adverse effects of any Colae semen containing products in the pharmacovigilance databases.

References

a) References relevant for the assessment:

Abalaka ME, Adeyemo SO, Okolo MO. Investigation into the medicinal values of *Cola* Species-*Cola Nitida* and *Cola Acuminata*. *Sci. Agric* 2015,10:31-34, in press, doi https://doi.org/10.15192/PSCP.SA.2015.10.1.3134

Adeosun OI, Olaniyi KS, Amusa OA, Jimoh GZ, Oniyide AA. Methanolic extract of *Cola nitida* elicits dose-dependent diuretic, natriuretic and kaliuretic activities without causing electrolyte impairment, hepatotoxicity and nephrotoxicity in rats. *Int. J. Physiol. Pathophysiol. Pharmacol* 2017, 9:231-239

Adisa WA, Otamere HO, Osifo CU, Idonije OB, Nwoke EO. Effects of aqueous extract of kola nut (*Cola Nitida Rubra*) on reproductive hormones in rats. *Niger. J. Physiol. Sci. Off. Publ. Physiol. Soc. Niger* 2010, 25:121-123

Aprioku JS, Clement EO. Subchronic *Cola acuminata* seed exposure: effects on body weight and male reproductive parameters in rats. *J. Reprod. Infertil. (Dubai, United Arab Emirates)* 2018, 9:20-27, in press, doi https://doi.org/10.5829/idosi.jri.2018.20.27

Aprioku JS, Kari FE. Spermatic effects of short-term administration of aqueous *Cola acuminata* seed extract in Wistar albino rats. *Eur. J. Biomed. Pharm. Sci* 2018, 5:998-1002

Bisong SA, Mfem CC, Nku CO, Ajiwhen IO, Osim EE. Long-term consumption of kola-nut (*Cola nitida*) diet does not increase anxiety related behaviour in mice. *Asian J. Res. Med. Pharm. Sci* 2019, 6, AJRIMPS 45797, in press, doi https://doi.org/10.9734/ajrimps/2019/45797

Emmanuel EU, Ebhohon SO, Adanma OC, Edith OC, Florence ON, Chioma I, *et al*. Acute toxicity of methanol extract of *Cola nitida* treatment on antioxidant capacity, hepatic and renal functions in wistar rats. *Int. J. Biochem. Res* 2016, Rev. 13, No pp. given, in press, doi https://doi.org/10.9734/IJBCRR/2016/28593

Erukainure OL, Oyebode OA, Sokhela MK, Koorbanally NA, Islam MS. Caffeine - rich infusion from *Cola nitida* (kola nut) inhibits major carbohydrate catabolic enzymes; abates redox imbalance; and modulates oxidative dysregulated metabolic pathways and metabolites in Fe^{2+}- induced hepatic

toxicity. *Biomed. Pharmacother* 2017, 96:1065-1074, in press, doi https://doi.org/10.1016/j.biopha.2017.11.120

Erukainure OL, Sanni O, Ijomone OM, Ibeji CU, Chukwuma CI, Islam MS. The antidiabetic properties of the hot water extract of kola nut (*Cola nitida* (Vent.) Schott & Endl.) in type 2 diabetic rats. *J. Ethnopharmacol* 2019, 242, in press, doi https://doi.org/10.1016/j.jep.2019.112033

Ishola IO, Ikuomola BO, Adeyemi OO. Protective role of Spondias mombin leaf and *Cola acuminata* seed extracts against scopolamine-induced cognitive dysfunction. *Alexandria J. Med* 2018 54:27-39, in press, doi https://doi.org/10.1016/j.ajme.2016.08.001

Nku CO, Ikpi DE, Udo EL, Okon UA. Effect of chronic consumption of *Cola nitida rubra* (kola nut) diet on biliary secretion and composition in albino wistar rats. *Res. J. Pharm. Biol. Chem. Sci* 2014, 5:1508-1514, 7 pp

Obidike IR, Aka LO, Ezema WS. Effects of caffeine extract from kola nut on body weight, hematology, sperm reserve and serum enzyme activities in albino rats. *Comp. Clin. Path* 2011, 20:625-630, in press, doi https://doi.org/10.1007/s00580-010-1045-y

Oboh G, Nwokocha KE, Akinyemi AJ, Ademiluyi AO. Inhibitory effect of polyphenolic-rich extract from *Cola nitida* (Kolanut) seed on key enzyme linked to type 2 diabetes and $Fe^{(2+)}$ induced lipid peroxidation in rat pancreas *in vitro*. *Asian Pac. J. Trop. Biomed* 2014, 4:S405-12 in press, doi https://doi.org/10.12980/APJTB.4.2014C75

Ogundipe JO, Afolabi OA, Saka OS. Effect of Crude and Decaffeinated Extracts of *Cola nitida* Seeds on Male Reproductive System in Swiss Albino Rats. *J. krishna Inst. Med. Sci. Univ* 2016, 5:10-17

Sangodele J, Okere S. PHYTOCHEMICAL CONSTITUTENTS AND HYPOGLYCEMIC PROPERTY OF *COLA ACUMINATA* SEED ON ALLOXAN-INDUCED DIABETIC RATS. *Basic Clin. Pharmacol. Toxicol* 2014, 115: 141

Udebuani AC, Otitoju O, Akaniru CN, Nwaogu LA, Abara PN. Effects of chronic consumption of *Cola nitida* on melatonin and enzyme production in albino Wistar rats. *Pharm. Lett* 2017, 9:7-15

Umoh IO, Emmanuel OA, Nna VU. Aqueous seed extract of *Cola nitida rubra* reduces serum reproductive hormone concentrations and sperm count in adult male albino Wistar rats. *Niger. Med. J.* 2014, 55:456-459, in press, doi https://doi.org/10.4103/0300-1652.144694

b) References that justify the need for the revision of the monograph:

None

Rapporteur's proposal on revision

☐ Revision needed, i.e. new data/findings of relevance for the content of the monograph

☒ No revision needed, i.e. no new data/findings of relevance for the content of the monograph

HMPC decision on revision

☐ Revision needed, i.e. new data/findings of relevance for the content of the monograph

☒ No revision needed, i.e. no new data/findings of relevance for the content of the monograph

The HMPC agreed not to revise the monograph, assessment report and list of references on *Cola nitida* (Vent.) Schott et Endl. and its varieties and *Cola acuminata* (P. Beauv.) Schott et Endl., semen, by consensus.