LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

# Public Assessment Report
# Scientific discussion

# Nipenesin
# (guaifenesin)

# SE/H/2090/01/DC

**This module reflects the scientific discussion for the approval of Nipenesin. The procedure was finalised on 2021-07-27. For information on changes after this date please refer to the module 'Update'.**

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# I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Nipenesin, 20 mg/ml, syrup in sachet.

The active substance is guaifenesin. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Nipenesin, 20 mg/ml, syrup in sachet, is submitted according to Article 10a of Directive 2001/83/EC. The applicant, McNeil Sweden AB, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and BE, DK, IE and LU as concerned member states (CMS).

**Potential similarity with orphan medicinal products**
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

# II. QUALITY ASPECTS

## II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

## II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

# III. NON-CLINICAL ASPECTS

**Pharmacology**
Guaifenesin is used as an expectorant indicated for providing temporary symptomatic relief from congested chests and coughs which may be due to a cold, bronchitis, and/or other breathing illnesses. The primary pharmacodynamic function/effect of guaifenesin is to increase the flow of less viscous gastric secretions that subsequently promote ciliary action. The viscosity, surface tension and adhesiveness of the secretions become reduced, leading to that mucus becomes easier to be expelled with coughing and dry doughs change to coughs that are more productive and less frequent. The non-clinical information on the pharmacology (primary and secondary pharmacodynamics) is very limited.

A study in Han Wistar rats demonstrated that there was no increase in respiratory secretion after IV administration (1.5x greater systemic exposure than after oral intake and absorption) and that abdominal surgery eliminated the effect of guaifenesin although it did not change systemic absorption. This indicates that the expectorant action of guaifenesin is mediated by stimulation of the gastrointestinal tract and not directly by the systemic exposure to the drug. Guaifenesin has also been reported to stimulate neurite outgrowth (rat DRG cells) and ameliorate motor nerve conduction velocity slowing in a diabetic type I mouse model. The implications of the latter neural effects are unclear with regard to the respiratory effects.

No secondary pharmacodynamics or safety pharmacology information is available. Considering the long clinical experience with guaifenesin, this is considered acceptable.

**Pharmacokinetics**
Only limited non-clinical pharmacokinetics information for guaifenesinis exists. The available data is generated in a rat animal model. Guaifenesin is is readily absorbed from the gastrointestinal tract in rat. When administered by various routes including intravenous (IV) bolus, oral gavage (50 mg/kg bw, 25 mg/ml) and gastric, jejunal or cecal infusions (50 mg/kg bw, 50 mg/ml), guaifenesin achieved a maximum plasma concentration (Cmax) of 15– 33 μg/ml. The time to reach Cmax (Tmax) in rats was faster when given as an oral bolus (27 min) than with gastric, jejunal or cecal infusions (120 min). In rats, the bioavailability of Guaifenesin for all gastrointestinal(GI) routes was ~70% and the terminal half-life of IV administration (~45 min) was identical to that associated with various GI routes of administration (45– 54 min).

No specific information has been provided on distribution. Guaifenesin is rapidly metabolized into various glucuronates & sulfate metabolites. A dominant metabolite is B-(2-methoxyphenoxy) lactic acid. All of these metabolites are eliminated via the urine which seems to be the main elimination route.

**Toxicology**
Only limited toxicological information is available for guaifenesin, mainly from acute toxicity and teratology rat studies. Based on old acute toxicity studies using different exposure routes, rats are most sensitive to guaifenesin exposure via the intravenous route (LD50 360mg/kg) and least sensitive to intramuscular exposure (4000mg/kg) (intravenous > intraperitoneal > oral > subcutaneous > intramuscular). Mice show the same sensitivity profile. Rabbits seem to be more tolerant than rodents to acute oral high dose exposure based on an LD50 of 1510mg/kg (rat), 690mg/kg (mouse) and 2553mg/kg (rabbit). No repeat-dose toxicity, genotoxicity or carcinogenicity information is available.

Regarding reproductive/developmental toxicity, only limited teratological information from rat is available. In a pilot rat study (using n=5 dams per group) with an exposure range between 250mg/kg and 600mg/kg (oral exposure between Gd6 and Gd17, observation at GD20), there was statistically significant maternal toxicity (reduced weight and food/water intake but no mortality) from the lowest dose. Embryofoetal toxicity was also observed from the lowest dose. Embryonic mortality was observed from 350mg/kg. There was a statistically significant reduction in foetal size from the low dose (reduction in foetal weight, body length, skull length, forelimb and hindlimb length and tail

length at ≥250mg/kg). Forelimb and hindlimb malformations (dropping wrist/ankle, 21-33% of foetuses) and tail malformations (kinky tail, 10-15%) were found at ≥500mg/kg. Across experimental exposure groups, 21.2%, 45.4%, 67.2%, and 86.9% of the foetuses demonstrated haemorrhagic spots (i.e., ≥250mg/kg). A skeletal staining assessment found that that there was increased intercostal space and improper development of carpals, metacarpals, tarsals, and metatarsals at the high dose (600mg/kg). LOAEL at 250mg/kg for maternal and embryofoetal effects (no NOAEL). As no toxicokinetic information was available in this study, there is some uncertainty how these doses relate to clinical exposure. The applicant has not provided any discussion on the relevance of the results (i.e., that would reduce the relevance of the study sufficiently to ignore it altogether). The applicant notes that the available pharmacokinetic data on guaifenesin indicates that the Cmax and AUC after oral dose of 50 mg/kg in rat is around 33.3µg/ml and 2469µg x min/mL (corresponding to a 14x margin compared to human exposure from 400mg dose in adults administered every 4 hours in a day). A dose of 250mg/kg (the low dose embryofoetal LOAEL in the rat study) would therefore very likely have a much greater margin. That being said, in the absence of a NOAEL value from the rat study, a 'safer' margin estimate based on the pharmacokinetic data is not possible. Overall, while the pilot study is suboptimal and therefore not fully conclusive, in the absence of any clear methodological reason to disregard the reported outcomes, the absence of NOAEL plus clear growth retardation and embryolethality effects from the lowest doses (250-350mg/kg) makes the pilot study results sufficiently relevant for an SmPC 5.3. notation (which also has been incorporated by the applicant). This conclusion is also in line with the applicant's statement in SmPC 4.6. that Nipenesin is not recommended during pregnancy and in women of childbearing potential not using contraception (which needs to be supported by clinical or non-clinical data).

Considering that the proposed usage is for patients aged 12 years and older, juvenile toxicity studies are not considered necessary. No local tolerance or other toxicologically relevant information is available.

**Environmental Risk Assessment (ERA)**
Guaifenesin belongs to the anisole compounds. Little to no experimental information is available for guaifenesin (CAS #93-14-1). A log Kow value of 1.39 (from an database entry) has been provided. A justification for not conducting a detailed ERA (Phase I and Phase II) has been provided. Based on that the active substance is a relatively common components in medical (human and veterinary) and non-medical products (cosmetic components, food additive, diagnostic agent), it is very unlikely that the generic drug addition of Nipenesin will increase overall environmental exposure (based on the CHMP ERA guideline framework from 2006).

**Conclusion**
There are no issues with the dossier from a non-clinical perspective.

# IV. CLINICAL ASPECTS

**Pharmacokinetics**
*Absorption*

Guaifenesin is well absorbed from the gastro-intestinal tract following oral administration, although limited information is available on its pharmacokinetics. After the administration of 600 mg guaifenesin to healthy adult volunteers, the Cmax was approximately 1.4 ug/ml, with tmax occurring approximately 15 minutes after drug administration.

*Distribution*

No information is available on the distribution of guaifenesin in humans.

*Biotransformation and elimination*

Guaifenesin appears to undergo both oxidation and demethylation. Following an oral dose of 600 mg

guaifenesin to 3 healthy male volunteers, the t½ was approximately 1 hour and the drug was not detectable in the blood after approximately 8 hours.

*Special Populations*

Adolescents (aged 12-17) showed similar exposure and $t_{½}$ as adults.
No information regarding guaifenesin's pharmacokinetics in other special populations is available.

*Interactions*

No interaction studies have been performed showing an interaction with guaifenesin.

Assessor's overall conclusions on pharmacokinetics

This is an application according to Article 10a well-established use. For a WEU application establishing a link between the applied for product and the literature data used to support efficacy and safety is crucial. In the studies supporting efficacy and safety several different guaifenesin formulations has been used (IR formulations, both syrup and tablets, as well as different ER-formulations). The proposed product is part of the Applicant's ongoing product development strategy to develop a range of formulations suitable for self-medication and it is essentially the already approved cough syrup contained in sachets instead of a bottle. The proposed formulation will only differ from the currently marketed formula by containing a reduced level of the preservative (Sodium benzoate) from 20 mg/10 ml to 10 mg/10ml and change in liquid excipient from 69% to 67% dry weight of sucrose. The amount of water balances those changes. It is agreed with the Applicant that this will not affect the PK, efficacy or safety of the product. A bridge to the literature is considered sufficiently established for the proposed product.

As this is a complete application, the bibliography should cover all aspects of pharmacokinetics needed to make a complete characterisation of the disposition of the compound. There appears to be limited pharmacokinetic data for guaifenesin published in the public domain, in particular for the syrup formulation whereas more recent publications are available for both IR and ER tablets. This lack of basic PK-information for guaifenesin is reflected in the SmPC of both the proposed product and other approved guaifenesin-containing products on the EU market. From a pharmacokinetic perspective the application is approvable.

**Pharmacodynamics**

Investigations of the pharmacodynamics of guaifenesin began already in the 1940-1950s. Several suggestions regarding the pharmacodynamics has been brought forward, however to this date no consensus on the exact mechanism of action has been established. Literature data also suggests that the formulation as such could contribute to the overall effect. Overall, it can be concluded that the provided literature supports an expectorant action of guaifenesin.

**Clinical efficacy**

For a well-established use (WEU) application, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use for the claimed therapeutic indication within the Union for at least ten years, with recognized efficacy and an acceptable level of safety. Important information in this regard is that guaifenesin has been approved as a medicinal product indicated for productive cough in Sweden at since 1974. Guaifenesin oral syrups are also marketed in several other EU-states.

The applicant has included nine clinical efficacy studies from the literature relevant to the use of guaifenesin in the treatment of cough. The studied populations and efficacy endpoints are heterogenous.
The applicant referred to placebo-controlled trials reported that guaifenesin was superior to placebo regarding improvement of cough symptoms but there was no difference in the efficacy guaifenesin

with regard to cough frequency, sputum rheology, subjective cough symptoms, and mucociliary and cough clearance.
In addition, systematic reviews showed that there was no supporting evidence for or against the use of guaifenesin for the symptomatic relief of cough.

The inclusion of negative publications supports the view that a thorough literature review has been performed. Included studies are considered to support the WEU-criteria regarding the degree of scientific interest in the use of the substance, as reflected in the published scientific literature and in large there is a coherence in the reported efficacy data.

The applicant has also retrieved clinical studies related to use in the adolescent population. Two out of three studies reported positive efficacy findings. It is noted that approval is sought for adolescents >12 years of age. There is no biological rationale as to why adolescents would differ from adults from a pharmacodynamic point of view and the reported findings are in line with findings in the adult population. Moreover, currently approved guaifenesin containing medicinal products in Sweden are indicated for use in the adolescent population.

Overall, although efficacy findings are deemed weak, included studies are considered to support the WEU-criteria regarding the degree of scientific interest in the use of the substance as reflected in the published scientific literature and the coherence of scientific assessments. The WEU criteria regarding the time over which a substance has been used with regular application in patients; quantitative aspects of the use of the substance, taking into account the extent to which the substance has been used in practice, the extent of use on a geographical basis and the extent to which the use of the substance has been monitored by pharmacovigilance or other methods are currently supported to a sufficient degree.

The assessor notes that a guaifenesin containing medicinal product with identical indication and posology, named Nipenesin is currently approved in Sweden.

**Clinical safety**
The first registration of a guaifenesin containing medicinal product was in 1972, i.e. 48 years ago. Presented sales figures from 2004-2019 supports the WEU criteria of a long-standing and wide-spread use.
The ADRs from clinical trials and epidemiology studies are in accordance with post-marketing experience, literature and cited databases. However, it is known that the vast majority of ADRs occurring in clinical practice are not reported, thus frequencies are difficult to estimate based on spontaneous reporting. Therefore, it is agreed that as proposed by the applicant, “not known” should be used in the SmPC section 4.8.

A presented fatal case related to a guaifenesin intoxication. According to the authors, at high doses guaifenesin causes depression of the central nervous system and is used as a muscle relaxant with sedative effects in veterinary medicine. The amount ingested in the present case is undetermined, the decedent’s significant other estimated that the number of tablets to ten, though such a low quantity appeared unlikely considering the subsequent presentation. The patient died in the ER from cardiac despite medical efforts. No anatomic contributor to the mechanism of death could be determined. Interestingly, none of the other reports of excess intake of guaifenesin mentions adverse cardiac effects, despite intake of large amounts, sometimes repeated over days.
The applicant is advised to closely monitor for signals related to adverse cardiac reactions, muscle relaxing, CNS-depressant effects and fatal cases. For a product intended for the OTC-setting, evidence of severe cardiac toxicity related to overdose, would lead to withdrawal from the OTC-market. However, currently no regulatory actions are recommended based on the single fatal case presented.

There is a large body of literature evidence which supports the association between overdose of guaifenesin and the development of kidney stones. The proposed wording in the SmPC, section 4.9 is therefore agreed.

There is limited information related to use in pregnancy. Adequate information is given in the SmPC section 4.6.

Overall, the presented safety data is considered acceptable for the intended short-term symptomatic use. Currently proposed recommendations in the SmPC regarding use; “if the symptoms persist or get worse, or if new symptoms occur, the advice is to stop using product and refer to physician” and “if cough persists for more than 7 days, tends to recur, or is accompanied by a fever, rash, or persistent headache, a physician should be consulted” are accepted.

**Risk Management Plan**
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Nipenesin.

Safety specification

| | |
|---|---|
| Important identified risks | None |
| Important potential risks | None |
| Missing information | None |

According to the applicant, known risks for guaifenesin require no further characterisation and are followed up through routine pharmacovigilance and for which the risk minimisation messages in the Product Information are adhered by prescribers. In the frame of GVP Module V Rev 2, these risks are considered to no longer fall within the scope of the definitions of important identified and potential risks and missing information and, therefore, not included in the list of safety concerns for this RMP.

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 1.0 signed 15 July 2020, is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

# V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Benylin Mucus Cough Warming 100 mg/5 ml Syrup, BE/H/0302/001 and BE/H/0303/001. The bridging report submitted by the applicant has been found acceptable.

# VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

According to the WEU-criteria, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use for the claimed therapeutic indication within the Union for at least ten years, with recognized efficacy and an acceptable level of safety. Important information in this regard is that guaifenesin has been approved as a medicinal product indicated for productive cough in Sweden at since 1974.
The efficacy data related to guaifenesin is deemed weak as presented in the literature review. Importantly, the weak efficacy data is balanced with presented safety data which indicates a benign safety profile with no alarming findings and it can be concluded that safety data is considered acceptable for the intended short-term symptomatic use in productive cough.
Overall, included studies are considered to support the WEU-criteria regarding the degree of scientific interest in the use of the substance as reflected in the published scientific literature and the coherence of scientific assessments. Therefore, the benefit-risk balance is considered positive and Nipenesin, 20 mg/ml, syrup in sachet, is recommended for approval.

**List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment**

N/A

**List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC**

N/A

# VII. APPROVAL

The decentralised procedure for Nipenesin, 20 mg/ml, syrup in sachet, was positively finalised on 2021-07-27.

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# Public Assessment Report – Update

| Procedure number* | Scope | Product Information affected (Yes/No) | Date of end of procedure | Approval/ non approval | Summary/ Justification for refuse |
|---|---|---|---|---|---|
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*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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