COMMERCIAL IN CONFIDENCE

TYPE OF APPLICATION: UK PLA (ABRIDGED)	
PROPOSED LICENCE HOLDER: Kabi Pharmacia, UK	
MANUFACTURER OF DOSAGE FORM: Kabi Pharmacia, Sweden	
LEGAL STATUS Prescription Only Medicine	**SALE/SUPPLY** Pharmacies and Hospitals

A nasal spray solution of 1% nicotine as an aid to the relief of tobacco withdrawal symptoms.

NUMBER: PL 00022/0141
PRODUCT NAME: Nicorette Nasal Spray 10mg/ml
THERAPEUTIC CLASS: Nicotine replacement
RECEIVED: 16 July 1993
MEETING: January 1994
COMMITTEE ON SAFETY OF MEDICINE
SUB-COMMITTEE ON CHEMISTRY, PHARMACY AND STANDARDS
CONSIDERATION BY OTHER COMMITTEES: Safety and Efficacy Sub-Committee
ASSESSED BY: **Pharmacy:** [redacted] **Pre-Clinical:** **Clinical:**

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[redacted]

ASSESSMENT REPORT
(ABRIDGED PRODUCT LICENCE APPLICATION)

LICENCE No: PL 00022 / 0141

PROPRIETARY NAME: Nicorette Nasal Spray 10mg/ml

COMPANY NAME: Kabi Pharmacia Ltd

ACTIVE(s): Nicotine, 10mg/ml

I. INTRODUCTION & BACKGROUND

A new route of administration for nicotine in a nasal spray formulation intended for the relief of tobacco withdrawal symptoms and hence as an aid to smoking cessation. A mechanical spray device delivers 0.5mg of nicotine per metered 50µl actuation, the recommended dose being one or two sprays to each nostril (a total dose of 1 to 2mg) as required (but no more than hourly) for up to 16 hours a day. A dose of 1mg nicotine is intended to achieve a rapid plasma nicotine level equivalent to smoking a low to medium strength cigarette.

Nicotine drug substance is obtained from [redacted]

The applicant holds licences for nicotine chewing gum and transdermal patches under the Nicorette brand, the most recently granted being for Nicorette Patches containing 5, 10 or 15mg nicotine (PL 00022/0103-5, granted 4 November 1992) and using nicotine from [redacted].

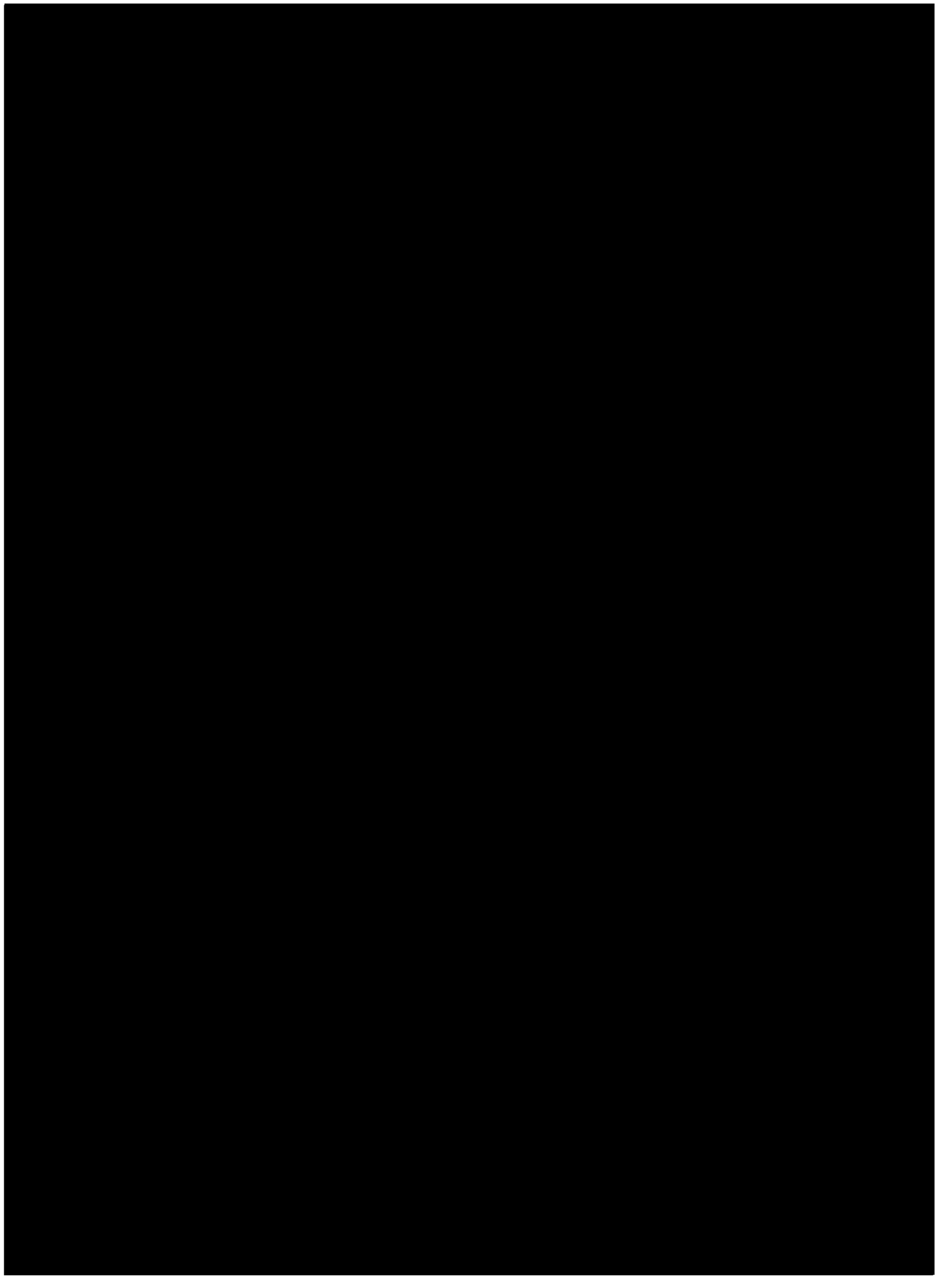
[redacted]

II. LEGAL STATUS

A Prescription Only Medicine (POM)

III. PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE



[redacted]

DOSAGE FORM

Formulation

Nicorette Nasal Spray is a [redacted] aqueous solution of nicotine base at 10mg/ml containing a parabens/disodium edetate [redacted] and a [redacted] β-ionone [redacted] with Polysorbate 80. It is presented in a mechanically

actuated nasal spray device (bottle, pump, adaptor and nose piece) which delivers 50µl of solution (0.5mg of Nicotine) per actuation to the nasal mucosa.

Each 10ml pack therefore contains the equivalent of 200 sprays which at the maximum recommended dosage (2mg per hour for a maximum of 16 hours per day) would provide enough solution for just over 3 days treatment. A 10ml pack contains a total of 100mg nicotine base; the fatal dose of nicotine for an adult is from 30 to 60mg (Martindale, 30thEd.)

[redacted]

Excipients

One non-pharmacopoeial material is used, [redacted] Aroma DZ 03226 [redacted]

[redacted]

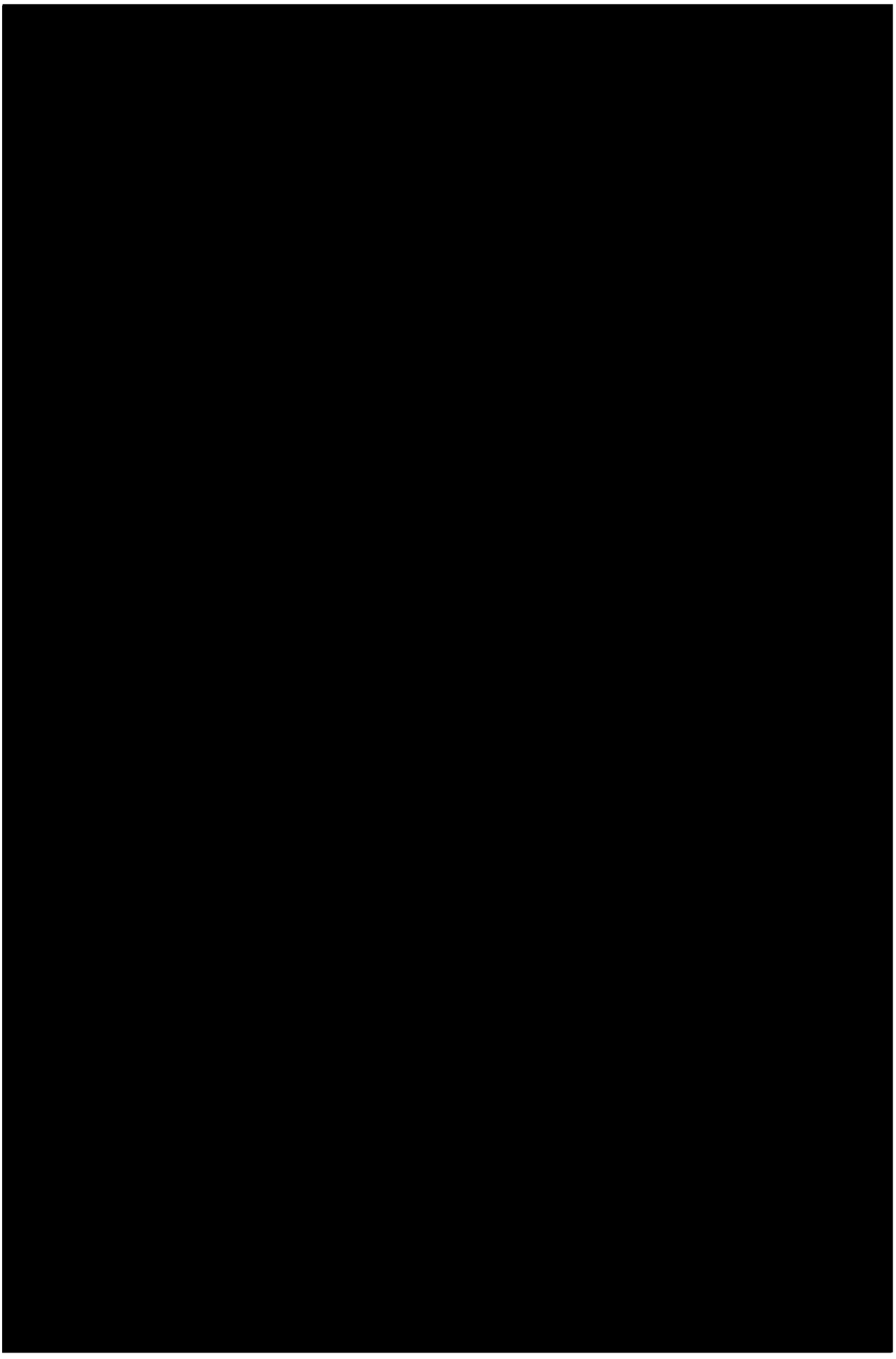
[redacted] also complies with EEC Directive 88/388 (Flavourings for

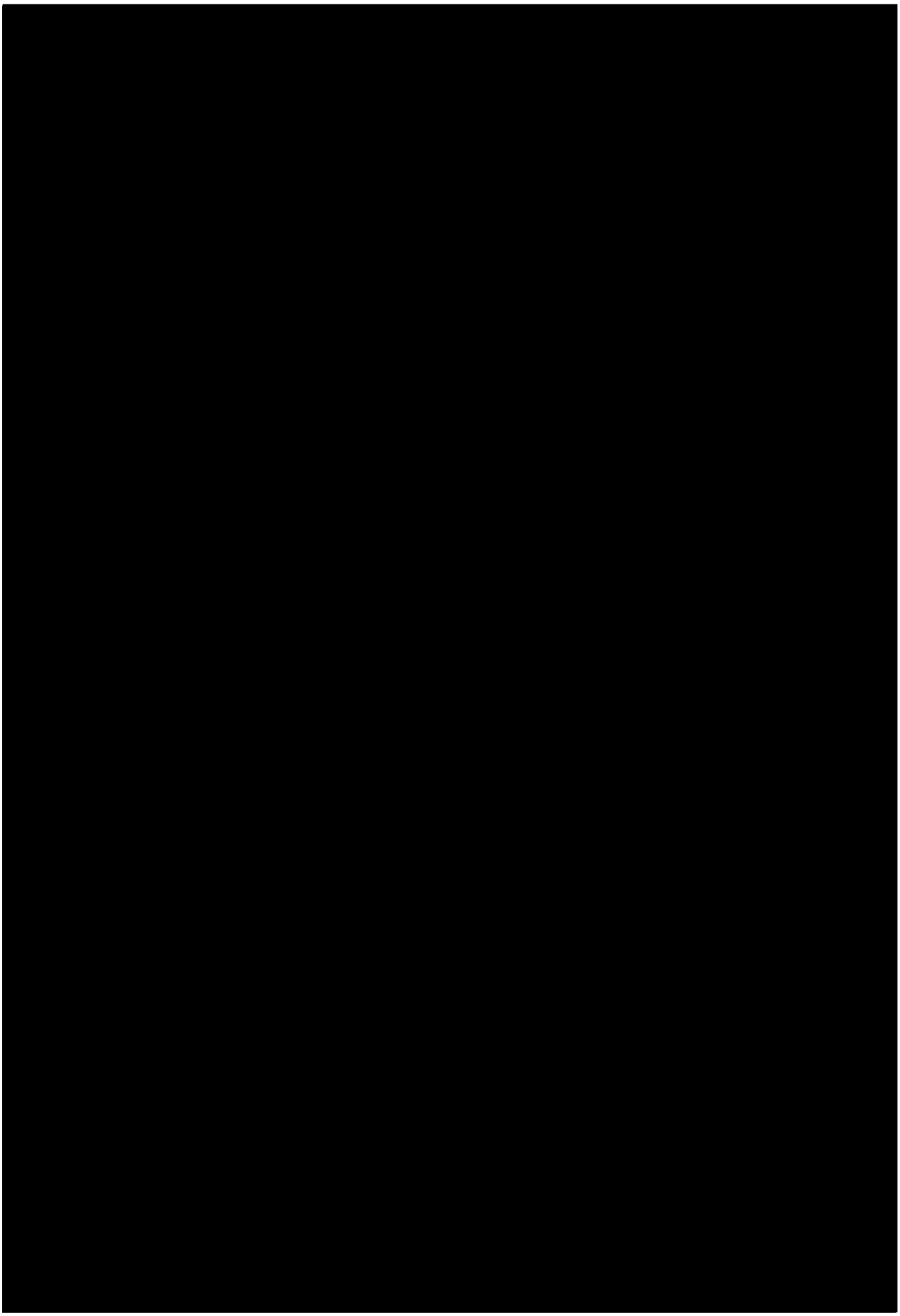
use in foodstuffs, etc..) [redacted]

All other excipients are required to conform to Ph.Eur specifications.

Immediate Packaging

The package presentation consists of a pump/adaptor crimped to an amber glass bottle with [redacted]





[redacted]

BIOAVAILABILITY

Nicotine is reported to be readily and rapidly absorbed through the skin and mucosa and metabolised, mainly in the liver, to cotinine and nicotine-N-oxide. A number of pharmacokinetic and bioavailability studies were carried out using male and female smokers as volunteers. Where their baseline nicotine levels during the study exceeded 4ng/ml, data were omitted from analysis on the basis that subjects had been taking a non-study source of nicotine. During the development and clinical phases a formulation without disodium edetate was used.

Pharmacokinetic & Bioavailability Studies

A pilot study in 5 volunteers confirmed rapid absorption but showed large inter-individual variations in C_{max}, t_{max} and AUC following a single dose equivalent to 1mg of nicotine. In another study in 8 volunteers, absolute bioavailability in comparison with an intravenous infusion varied between 50% and 80%, and no differences in bioavailability were seen between nasal application by spray, or by drops to the inferior nasal conchae or nasal septum.

A repeated dose study in 18 volunteers administered doses of nasal spray each equivalent to 1mg nicotine at hourly intervals for 7 hours and monitored blood levels for up to 6 hours after the last dose. An accumulation ratio of 3.14 was found when comparing the mean C_{max} following the 7th dose with that following the 1st dose.

A further absolute bioavailability study was conducted on 8 volunteers who were given the equivalent of 1mg of nicotine from the proposed marketed formulation hourly for 11 hours, and in comparison a dose of 2mg of nicotine given as an infusion over 20 minutes. A comparison of the dose-corrected AUC values for nasal spray (period 10 to 11) and infusion showed an absolute bioavailability for the spray of 56% ± 17%.

Bioequivalence Study

Disodium edetate, added to Nicorette Nasal Spray in a late formulation change [redacted], has been reported to exert a penetration enhancing effect on co-administered active substances. A bioequivalence study was necessary for comparison with the earlier formulation used in pharmacokinetic and clinical studies. The study was conducted with 18 volunteers using an open, intra-subject cross-over design. Subjects self-administered 1mg of nicotine (2 sprays) hourly for eleven hours using either the proposed marketing formulation with disodium edetate, or a research formulation without disodium edetate. The 90% confidence intervals for ratios of AUC_{10-11} were 0.94-1.11 and for C_{max} were 0.94-1.09, and hence both ratios were within the ranges accepted as demonstrating bioequivalence and no penetration-enhancing effect of disodium edetate was evident.

A validated [redacted] method was used for the analysis of nicotine and cotinine in blood plasma samples with the following limits:

[redacted]

PRODUCT PRESENTATION

Labelling

Considering the frequency of use, the outer carton (which has the full labelling details) may well be quickly discarded. The bottle label has only a minimum of information. The bottle however is of sufficient size that complete labelling details could be included legibly on its label without the need for small container exemptions usually applicable to single dose units. An amended bottle label text should be proposed to include information similar to that for the carton label.

Label details should include a statement giving the amount of active ingredient per dose volume unit (ie. per actuation of 50µl.)

The label statement mentions the need for protection from strong light, but this should be amended to be consistent with details supplied in the SPC, Data Sheet and the MLA form which refer to the need to protect from light, ie. any light.

A suitable label statement should be proposed warning that the product should be discarded after a period of time from first opening, or the omission of such a statement justified by reference to data on stability in part-used containers.

Patient Information

A detailed "Guide for Patients" leaflet is proposed including Directions for Use. In this section patients are instructed to prime the spray before use by pressing "several times firmly and quickly until a fine spray appears". A warning statement would be appropriate here to direct the priming sprays away from the eyes.

The dip-tube design of the package means a certain amount of solution may still be present in used containers; advice on safe disposal should be included.

The instruction regarding protection from strong light is not consistent as mentioned above under Labelling.

IV ASSESSOR'S CONCLUSIONS

The Committee may wish to consider that the following issues should be addressed by the applicant:

[redacted]

[redacted]

Part V SPECIAL PARTICULARS

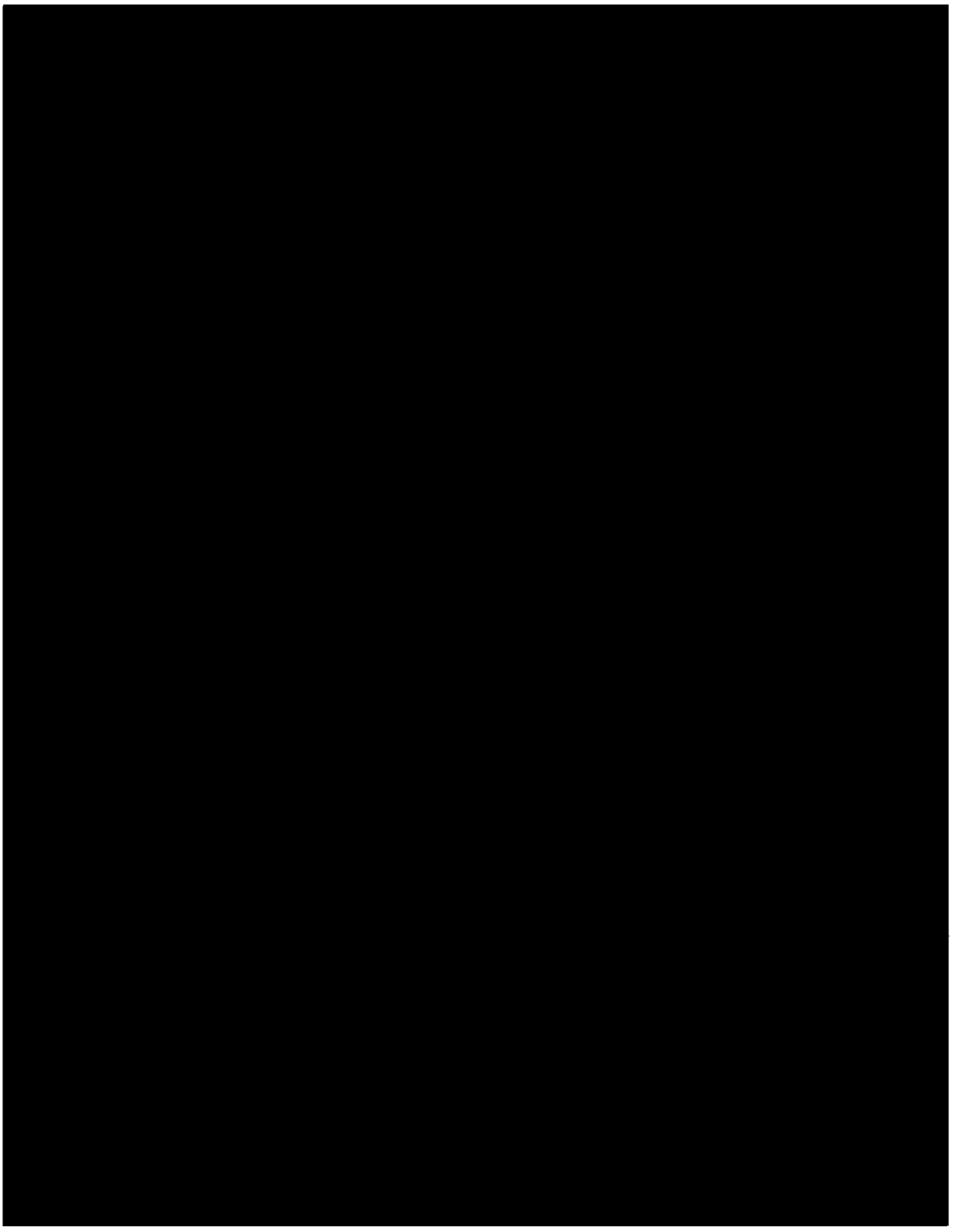
12. Amended labelling should include:
    12.1 A statement of nicotine content per volumetric dose unit
    12.2 Consistent storage instructions regarding protection from light
    12.3 A warning regarding the in-use shelf-life of part used containers.

13. Amended labelling for the primary container should include information similar in extent to that on the carton label consistent with legibility.

14. Suitable warning statements in the Directions for Use should be proposed concerning:
    14.1 The need to direct priming sprays away from the eyes
    14.2 Advice on safe disposal of part-used containers.

[redacted]

Pharmaceutical Assessor: [redacted]



ABRIDGED PRODUCT LICENCE APPLICATION

MEDICAL ASSESSMENT

1. INTRODUCTION

This application is for a novel dose form for nicotine which was designed to be used intranasally. It is presented as a nicotine solution in a glass bottle with a manual pump spray, dose metering, delivery system which, having been primed, is placed inside each nostril in turn and sprayed.

2. BACKGROUND

A number of formulations of nicotine containing products have been licensed, these include a variety of different transdermal delivery systems and two flavours of chewing gums. It should be noted that the medicinal products, containing nicotine as the sole active substance (gum and patches) and currently licensed, were approved for the treatment or relief of nicotine withdrawal symptoms associated with the cessation or abstinence from smoking in nicotine dependent persons. The basis for this was the fact that 'nicotine dependence' could be classified as a smoking related disease and that withdrawal of the alkaloid in question was associated with well documented quantifiable multi-organ physiological phenomena. The use of tobacco products in particular 'smoking' had not been classified as a disease, thus medicinal products could not be used in its 'treatment'. It was also recognised at the time of licensing the patches that some form of behavioural modification support should be provided as an essential component of the treatment of this particular drug dependence. The rehabilitation of habitual element of smoking was regarded as another important factor.

3. INDICATIONS

The claimed indications are "*a treatment aid to smoking cessation for the rapid relief of tobacco withdrawal symptoms. It may be of particular use in heavily dependent smokers*".

The claimed indication fails to adequately recognise the disease state for which nicotine containing medicinal products should properly be used i.e. primarily the treatment of nicotine withdrawal symptoms in nicotine dependent persons. An alternative form of words should be considered for the claimed indications e.g. - for the relief of nicotine withdrawal symptoms associated with cessation of smoking, in nicotine dependent persons.

The statement concerning use in heavy smokers is not an indication and therefore should be deleted as it is not within the published recommendations for describing indications.

4. DOSE & DOSE SCHEDULE

The recommended dose and dose schedule is:

"*Children: Not for use by children*

Adults (including the elderly): The spray should be administered according to the package insert. Counselling should take place also, if available. It is recommended the patient uses the spray when required, with a recommended level of 1 or 2 sprays to each nostril per hour. Each spray delivers 0.5 mg of nicotine, about half of which enters the circulation.

Dosage should not exceed 2 sprays to each nostril per hour for 16 hours per day, (maximum 13 with 2mg per 24 hours).

The recommended period of treatment is 3 months as follows:

(a) Over 8 weeks dosage should be as required within the limits set out above.

(b) Over the following 4 weeks the usage should be gradually reduced, 2/3rds dosage being used for 2 weeks (or a limit of 1 spray per nostril per hour). Over the final 2 weeks the usage should further taper off with 1/3rd the original usage or a limit of 1 spray to only 1 nostril per hour.

If the patient relapses, the physician may judge whether a full further course is justified, coupled with full counselling."

The recommendations should contain a specified age limit of 18 years as this was the limit stated in some of the recently licensed nicotine products.

The dosing recommendations for this potent addictive alkaloid containing product might be considered a cause of concern in terms of both safely and efficacy in use, particularly as it's recommended for ad libitum dosing and there is clear evidence of chronic (one year) high frequency use in persons who quit smoking within the first two weeks of the start of use of the product. Unlike the licensed nicotine products, appropriate advice on doses for different categories of smoker was not provided. The references to heavy smokers in the claimed indications did not constitute adequate advice in the context of dosage. The recommendations failed to advise on the matter of sniffing during or after activating the spray, a small percent of the aerosol appeared to pass distil to the nose and caused adverse events. The recommended duration of use was considered excessive and not fully supported by all of the evidence, the 3 month period should be considered as a maximum and not the norm. The proposed recommendations for reducing dosing over the final 4 weeks of use were not helpful nor were they particularly informative; by virtue of reference to fractions of doses to be used. The advice and references to counselling or other forms of behavioural support or habit rehabilitation therapy were insufficient to assure compliance .

5. TOXICOLOGY

A comprehensive review of the toxicology of nicotine was provided. Some new data were included from local tolerance studies in guinea pigs administered the nasal spray, nasally. A summary and discussion of the results of this work were included in the pre-clinical expert report. The human experiments were of adequate size to provide data on its acute and intermediate term hazard potential in clinical use.

It was noted that there was a lack of specific comment on the excipient β-ionone and its local effects on nasal mucosa. It recognised that this material is used as a food aroma/flavouring additive and in cosmetics. However the safety and efficacy of the parent β-ionone and its associated impurities in medicinal products remains to be adequately documented. Ionone has been used in perfumes and has been recorded as causing allergic reactions.

6. CLINICAL PHARMACOLOGY

The dossier contained a comprehensive review of the clinical pharmacology of nicotine and copies of the referenced published papers were supplied. A review of some of the various non-tobacco product, nicotine delivery systems was also provided in the dossier, these included licensed medicinal products.

Pilot study Five (5) healthy smokers were given a single dose of 1 mg nicotine in 100 µL of solution [redacted] sprayed into one nostril. Plasma samples were harvested initially at one minute and subsequently at longer intervals up to two hours, to determine the kinetic profile from this route of delivery. A wide inter-subject variation was observed.

The following pharmacokinetic values for nicotine were derived.

Subject	C_{max} (ng/mL)	T_{max} (min)	AUC (ng/mL *min)
1	6.00	4.00	469.50
2	8.90	15.00	635.10
3	7.70	7.00	603.25
4	8.30	30.00	498.90
5	16.50	4.00	965.10
Mean ± s.d.	9.48 ± 4.07	12.00 ± 11.02	634.37 ± 197.41

Study NNS88005 compared the absolute bioavailability of nicotine solution applied to different nasal regions (inferior nasal conchae, nasal septum) and as a nasal spray. Eight healthy, male (2) and female (6), subjects were exposed to the test materials, using an open, randomised, intra-subject, cross-over comparative experiment design. The nicotine solution strength was 10 mg/mL and it was administered to the selected local sites with a pipette or via the pump spray to the nasal cavity. The nicotine injection was given as a 0.07 ng/mL 10mL intravenous infusion over 2 minutes. From the observations and calculations submitted it would appear that the absolute bioavailability of nicotine was between 50 to 80% for the nasal administrations. The rate of absorption was high, C_{max} was reached within 10 minutes. No significant differences in the rate of absorption or availability were identified between the two local sites or the whole nasal cavity methods of administration.

See Appendix 1 on pages 42 - 42 for more detailed tables of results.

The following pharmacokinetic values (mean ± s.d.) for nicotine were derived.

Route	C_{max} (ng/mL)	T_{max} (min)	AUC_{inf} (ng/mL *min)
Intravenous	10.08 ± 6.58	5.00 ± 2.14	1076.41 ± 246.18
Nasal spray	8.10 ± 4.98	11.50 ± 11.8	904.85 ± 408.25
Drop nasal septum	9.16 ± 6.86	11.71 ± 10.08	1166.39 ± 516.44
Drop nasal conchae	7.24 ± 2.66	12.51 ± 8.45	966.06 ± 357.68

Study T91NI07 was a pharmacokinetic experiment with nicotine solution using 8 healthy smokers. An intravenous infusion of nicotine in a dose of 2 mg was given a period of 20 minutes. These same subjects subsequently participated in Study 92-NNNS-001 which is described below and from which absolute bioavailability for the nasal spray was calculated based on the results found in this intravenous study and the later spray study. The absolute bioavailability was estimated to be 56 ± 17% using the data from the two studies which were completed within months of each other.

Study 92-NNNS-001 compared the bioequivalence of two nicotine nasal spray formulations, one being that generally used in the clinical trial programme and a second which contained disodium edetate [redacted]. 18 subjects were used in the experiment during which doses of 1mg nicotine were given hourly for 11 hours. 8 of these subjects had previously participated in an intravenous kinetic study T91NI07. Whole blood samples were taken at what appeared to be appropriate intervals. The study was of an open, randomised, intra-subject cross-over comparative design. A second objective of this experiment was to demonstrate dose proportionality between single and dual sprays of the solution up one or both nostrils. The study would appear to have been conducted in a manner consistent with the principles of good clinical practice.

The following pharmacokinetic values (mean ± s.d.) for nicotine were derived.

Spray	C_{max} (ng/mL)	T_{max} (hr)	AUC (ng/mL *hr)
Original formulation	8.90 ± 3.41	10.24 ± 0.13	7.58 ± 2.97
New formulation	9.10 ± 3.30	10.22 ± 0.08	7.78 ± 2.75

Bioequivalence at steady state would appear to have been demonstrated on the basis of the results which showed that the values for the key pharmacokinetic parameters fell within the published guideline limits. The second element in this study was also satisfactorily demonstrated, namely dose proportionality between one and two sprays of the novel formulation.

See Appendix 2 on pages 44 - 48 for more detailed tables of results.

Study T 88NN01 was a pharmacokinetic experiment in 18 subjects exposed to seven hourly doses of 1 mg of nicotine delivered as two 50 µL nasal sprays. A mean steady state maximum plasma concentration of 8 ng/mL and an accumulation ratio of 3.1 were found and reported by the applicant. A mean plasma half life of 3.19 ± 0.60 hours was calculated.

The following pharmacokinetic values (mean ± s.d.) for nicotine were derived.

Spray	C_{max} (ng/mL)	AUC (ng/mL *hr)
Dose 1	3.50 ± 1.38	2.15 ± 0.92
Dose 7	8.55 ± 3.11	6.65 ± 2.45

In summary it would appear that about 50% of the active substance from a nicotine solution at a strength of 10 mg/mL was absorbed when delivered into the nasal cavity as a fine aerosol spray. Doses of 1 mg of nicotine delivered by this method and route, at regular hourly intervals, would appear to produce a steady state maximum plasma concentration of about 8.5 ng/mL.

7. EFFICACY

The evidence provided in support of the efficacy of the nicotine nasal spray was in part based on the evidence originally supplied in respect of the nicotine chewing gum and transdermal patches. In addition some original clinical trial work, which was conducted with nicotine solution delivered by nasal spray and reports of the outcome of these trials, were provided as evidence.

Study T89NN05 was a double blind, placebo controlled, parallel group clinical trial in a total of 157 subjects. The study was conducted by [redacted]. The active sprays used in this study were of a different formulation to that proposed for marketing. The active spray delivered 0.5mg nicotine in 50 µL of base per pump actuation. The placebo spray contained piperine, a substance isolated from black pepper and which is reportedly more toxic to the housefly than pyrethrum. A treatment dose was defined as one spray up each nostril delivering a total of 1.0 mg nicotine in 100 µL of base. Use of the spray was ad libitum, up to a maximum of 40 doses per day (40 mg nicotine), at a rate of up to 5 doses per hour (5 mg nicotine). It was reported that the average dose of nicotine absorbed by smoking a high nicotine cigarette was 1.14 mg and from a low yield cigarette 0.86 mg. [Feyerabend C et al. (1985)]

It was reported that 34% using active and 18% using placebo sprays were abstinent at week six. The abstinence rates at 3 months were 25% and 15% for active and placebo rexpectively. The report of this study provided in the dossier did not contain facts or comments on the results of all of the outcome measures which were in the protocol.

Study T89NN04 was a double blind, placebo controlled, parallel group clinical trial in a total of 248 subjects. The study was conducted by [redacted]. The active sprays used in this study were of a different formulation to that proposed for marketing. The placebo spray contained piperine. Some of the materials used in this study were from the same batches as used in the above study.

Spray use was documented throughout the total study period. Follow up was for one year during which time supply and use of the spray continued ad libitum. It would appear from the results presented that one third of subjects were regular users at three month and that one third of these were still users after a year. This prolonged usage by a small but significant number of subjects suggests that dependence to the drug delivered by this route does occur. This was supported by the facts in the listings of results which

showed that the majority of spray users at one year had actually stopped smoking by the defined limit of week 2 and remained abstinent for their remainder of the trial.

		ACTIVE SPRAY (N = 125)		PLACEBO SPRAY (N = 123)
TIME	N	DAILY SPRAYS Mean ± s.d.	N	DAILY SPRAYS Mean ± s.d.
2 Days	112	11.4 ± 7.9	107	14.7 ± 9.7
1 Week	97	12.4 ± 9.0	86	13.0 ± 9.5
2 Weeks	81	12.6 ± 8.7	63	11.8 ± 8.9
3 Weeks	80	13.3 ± 9.2	52	10.2 ± 8.8
4 Weeks	77	13.5 ± 9.6	38	10.1 ± 9.4
5 Weeks	70	13.9 ± 10.3	31	10.1 ± 10.6
6 Weeks	68	13.5 ± 9.8	28	7.7 ± 8.1
3 Months	39	11.8 ± 9.4	4	4.7 ± 2.1
6 Months	23	16.2 ± 9.0	0	
12 Months	13	14.1 ± 11.3	0	

See Appendix 3 on pages 49 - 54 for more detailed tables of results.

It is recognised by some experts working in the field of dependency "that ad libitum (PRN) schedules are thought to promote both behavioural and physiological dependence". [Hughes J R 1988]

Study T89NN02 (UK) was a placebo controlled, randomised, double-blind trial in a total of 228 male and female smokers, of whom 116 subjects were exposed to the nicotine spray. Where members of the same family or close friends volunteered to participate in the experiment they were assigned to the same group, reportedly to reduce the unblinding of treatments.

The objects of the study were defined as (1) "*to evaluate the safety and efficacy over one year of nicotine nasal spray as aide to smoking cessation in motivated patients* "and (2) "*to assess the uptake of nasal nicotine spray and its effect on the experience of tobacco withdrawal symptoms and weight gain after stopping smoking.*" The active dose was reported as "*one dose of NNS (1 mg nicotine) was administered intranasally as a 50 µL spray (0.5 mg nicotine) into each nostril. Use of the nasal sprays was ad libitum with instructions not to exceed 5 doses per hour (5 mg in active spray users) and 40 doses per days (40 mg nicotine)*". It was noted that this experiment had a number of additional objectives, with particular reference to nicotine dependence and withdrawal symptoms, which were not fully reported in the dossier.

Subjects were initially treated for 12 weeks with provisions for use of the spray to be continued for a year. Psychological support groups were and integral part of the trial. Subjects who used the spray for more than 6 months and any subject who experienced adverse reactions to the spray where designated as appropriate for specialist ENT examination. However no baseline examinations were conducted prior to treatment. Plasma nicotine, cotinine and carbon monoxide were monitored during the trial.

The results of this clinical trial were described by the applicant as follows:

Outcome	Visit	Active n = 116 (%)	Placebo n = 111 (%)	p
Completely abstinent all sessions from week 3	Week 8	57 (49)	23 (21)	<0.0005
	Month 3	48 (41)	19 (17)	<0.0005
	Month 6	37 (32)	13 (12)	<0.0005
	Month 12	30 (26)	11 (10)	<0.005
Completely abstinent all sessions from week 3 occasional slips allowed	Week 8	56 (56)	27 (24)	<0.0005
	Month 3	53 (46)	21 (19)	<0.0005
	Month 6	41 (35)	15 (13)	<0.0005
	Month 12	33 (28)	14 (13)	<0.005

There was reported less weight gain, over the year, in the active than the placebo group. An average gain of 6 Kg was observed in the placebo group which was almost double that seen in the active spray group. It was also reported that there was relief of the withdrawal symptoms associated with the use of the active spray. It was noted that at the end of one year 17% (19/111) of subjects were still using the active spray and that the frequency of use was almost twice that recorded at the start of the study. Of these persistent users 14/19 had been abstinent from smoking throughout the year.

It was evident that a significant number of subjects were persistent and frequent users of the active spray after one year. This would suggest that this particular product has the capacity to support a pre-existing dependence on a known addictive substance, the alkaloid nicotine. It was also reported that a highly significant number of subjects experienced mood altering effects during the first four weeks of nicotine spray use - on average about 60% experienced a calming effect, 48% felt more alert, 35% reported that the spray made them feel good or "high".

See Appendix 4 on pages 55 - 67 for more detailed tables of results.

Study T89NN03 (USA) was a placebo controlled, randomised, double-blind trial in a total of 255 male and female smokers, of whom 128 subjects were exposed to the nicotine spray. Members of the same household and close friends were not permitted in the study. The objectives of the study were described as (1) to determine if the nicotine spray enhances success rate over placebo and (2) to test relief of withdrawal as part of a smoking cessation trial. The active dose was one dose of NNS (1 mg nicotine) administered intranasally as a 50 µL spray (0.5 mg nicotine) into each nostril. Use of the nasal sprays was ad libitum with instructions not to exceed 5 doses per hour (5 mg in active spray users) and 40 doses per days (40 mg nicotine). It was also noted that this experiment had a number of additional objectives, with particular reference to nicotine dependence and withdrawal symptoms, which were not fully reported in the dossier.

Subjects were initially treated for 12 weeks with provisions for use of the spray to be continued for six months. Support measures were part of the trial, these included written materials and a standard video tape. Plasma nicotine and cotinine were measured during the trial.

The results were summarised as follows

Outcome	Visit	Active n = 128 (%)	Placebo n = 127 (%)	p
Completely abstinent all sessions from week 2	Week 6	74 (58)	41 (32)	<0.0005
	Month 3	59 (46)	25 (20)	<0.0005
	Month 6	41 (32)	18 (14)	0.001
	Month 12	31 (24)	12 (9)	0.002
Completely abstinent all sessions from week 2 occasional slips allowed	Week 6	87 (68)	53 (42)	<0.0005
	Month 3	72 (56)	37 (29)	<0.0005
	Month 6	49 (38)	26 (20)	0.002
	Month 12	36 (28)	17 (13)	0.004

See Appendix 5 on pages 68 - 78 for more detailed tables of results.

In summary the clinical studies using nicotine nasal spray and supportive behavioural modification therapy appear to have demonstrated that twice as many subjects were abstinent from smoking at the end of the study periods (e.g. 3 months and 12 months) when compared to placebo spray users. There was evidence from these studies that the withdrawal symptoms were less in those using active compared to placebo sprays.

Study T91NN03 (SW) was described by the applicant as "*a long-term study in hard core smokers*". It was designed as a randomised treatment trial with one group using the spray ad libitum and the second group using the spray at a fixed hourly dosing rate. 90 subjects who had failed to stop smoking while participating in previous trials of the nicotine transdermal product were recruited for this study. An initial interim analysis of results showed that 44/90 (48.9%) were abstinent at 6 weeks and 12/90 (13.3%) were abstinent at 6 months.

8. SAFETY

The were no serious adverse drug reactions as such reported in the dossier. However it would appear that the nicotine nasal spray is associated with a very high incidence of intense local adverse effects, particularly in the initial days of use. Local nasal irritation was experienced by up to 90% of users within the first two days of use, these effects were rated as subjectively severe or moderately severe. By contrast the equivalent rate for the piperine containing placebo was about 60%. The users rapidly became tolerant of this over the first few weeks. Sneezing was also a frequent event immediately following dosing. Runny nose, watering eyes, throat irritation, coughing all occurred more frequently at the start of treatment and gradually reduced as the weeks passed. The occasional minor nose bleeding was also noted, however there were no major episodes of profuse epistaxis.

The long term effects on nasal mucosa were uncertain, despite the limited number of clear reports on those who had ENT specialist examinations, as there were no baseline examinations of the organ in question.

A significant safety concern relates to the significant number of persistent spray users at the one year follow up, despite the fact that the majority of these chronic users had stopped smoking within the first two weeks of use. The spray system is one from which rapid overdosage could occur if used in association with other sources of nicotine.

Other side effects reported during the clinical trials were headache, dizziness, nausea and vomiting, lassitude and mood alterations. It was noted that some of the users reported experiencing a 'high' while using the active spray; this is a potential safety hazard in so far as it could contribute to abuse and induction of dependence with this addictive alkaloid.

See Appendix 6 on pages 79 - 86 for more detailed tables of results.

9. EXPERT REPORTS

The pre-clinical and clinical expert reports were signed by appropriately qualified persons who both appeared to be key members of the applicants development team for nicotine containing medicinal products.

See Appendix 7 on pages 87 - 123 for the full pre-clinical report.
See Appendix 8 on pages 124 - 154 for the full clinical report.

10. DATA SHEET (UK)

The draft data sheet text provided was consistent with the proposed terms of the licence. The proposed uses should be revised to properly reflect the medical treatment of nicotine dependent persons, references to heavily dependent smokers should be deleted. The dosage recommendations should be revised so as to provide more detailed dosing advice relative to the patients pre-existing tobacco usage. The treatment period should be presented as a maximum of three months and not as currently recommended so as to minimise the incidence of substituted dependence. The tapering of dose at the end of the treatment period should be described in more understandable terms. The product should be specifically contraindicated in children and persons up to the age of 18 years. Concomitant use of other licensed nicotine products should be proscribed. The advice in respect of driving and operating machinery should clearly state that 'the nasal spray should not be used while driving or operating machinery as sneezing and watering eyes can contribute to accidents and result in serious injury'.

11. PATIENT INFORMATION LEAFLET

The draft text of a patient information leaflet, as included with the application, was not completely satisfactory. It was consistent with the proposed terms of the licence. However, it should be revised to take note of the comments made in respect of the MLA201 presented below. It is noted that some of the safety advice in the patient leaflet is not contained in the proposed terms of the licence, this anomaly should be rectified References to alternative nicotine products as alternative therapies with the gum or patch constitutes a form of advertising and should be deleted. The descriptions of purpose of the spray should be revised in terms of withdrawal symptoms. The descriptions of unwanted effects do not properly reflect the initial intense local reactions

reportedly experienced by the majority of users and as described in the dossier. Patients should be warned of such phenomena even if they will develop tolerance to the discomfort within a short period of time.

See Appendix 9 on pages 155 - 159 for more detailed tables of results.

12. LABELLING

The draft labelling text and mock-up provided for the carton and bottle were essentially satisfactory.

13. MLA 201

The MLA 201, as it forms the proposed terms of the licence, should be revised so as to better reflect the target disease, to strengthen the contraindications in respect of young persons, to improve the dosage advice and to introduce tighter limits on duration of use. The proposed uses should be revised to properly reflect the medical treatment of nicotine dependent persons, references to heavily dependent smokers should be deleted in the absence of substantial evidence to support the statement. The dose and dosage schedule recommendations should be revised so as to provide more detailed dosing advice relative to the patients pre-existing tobacco usage. Full details of use should be stated in the section in dosage recommendations as cross-references to other non-licence documents are not sufficient. The treatment period should be presented as a maximum of three months and not as currently recommended so as to minimise the incidence of substituted dependence. The tapering of dose at the end of the treatment period should be described in more understandable terms. The product should be specifically contraindicated in children and persons up to the age of 18 years. Concomitant use of other licensed nicotine products should be proscribed. The advice in respect of driving and operating machinery should clearly state that 'the nasal spray should not be used while driving or operating machinery as sneezing and watering eyes can contribute to accidents which may result in serious injury'. A clear statement should be introduced on the occurrence of substituted dependence.

See Appendix 10 on pages 160 - 163 for more detailed tables of results.

14. SUMMARY OF PRODUCT CHARACTERISTICS (EC)

The draft summary of product characteristics text provided was consistent with the proposed terms of the licence. The proposed uses should be revised to properly reflect the medical treatment of nicotine dependent persons, references to heavily dependent smokers should be deleted. The dosage recommendations should be revised so as to provide more detailed dosing advice relative to the patients pre-existing tobacco usage. The treatment period should be presented as a maximum of three months and not as currently recommended so as to minimise the incidence of substituted dependence. The tapering of dose at the end of the treatment period should be described in more understandable terms. The product should be specifically contraindicated in children and persons up to the age of 18 years. Concomitant use of other licensed nicotine products should be proscribed. The advice in respect of driving and operating machinery should clearly state that 'the nasal spray should not be used while driving or operating

machinery as sneezing and watering eyes can contribute to accidents and result in serious injury'.

See Appendix 11 on pages 164 - 169 for more detailed tables of results.

15. DISCUSSION

The evidence provided in respect of the clinical pharmacology of the nicotine nasal spray demonstrated that the active substance was absorbed by the nasal mucosa and that plasma levels of nicotine sufficient to alter withdrawal symptoms could be achieved. It was also shown that bioequivalence between the formulation used in the development programme and that proposed for marketing could be demonstrated within the limits as stated in the published guidelines. The clinical trials of the product provided evidence that about 40% of subjects using the active spray were still abstinent from smoking at three months compared to about 20% of placebo spray users. These results were reduced by half when subjects were followed up to one year. There was a significant incidence, 10%, of substituted dependence recorded throughout the clinical trial programme. The majority of persistent users at one year had already stopped smoking by week two of their respective trials. There was a very high incidence of local adverse reactions on initiation of therapy to which tolerance developed in a matter of days.

Overall the evidence provided would appear to have shown that the nicotine nasal spray can produce plasma levels consistent with that necessary to relieve nicotine withdrawal symptoms; it supported nicotine addition in a significant proportion of spray users; it was associated with significant local adverse events particularly on initiation of therapy and it may constitute a hazard associated with driving or using dangerous machinery. The proposed ad libitum use could encourage abuse in respect of both overdose and addiction. It is clearly a medicinal product for which the approved methods for sale and supply should only be on prescription. The legal status for this specific product should be as a prescription only medicine. In view of the dependence factor associated with this product and its active ingredient a more intensive level of control on its supply may be appropriate.

16. ASSESSOR'S CONCLUSIONS

The committee may wish to consider the evidence provided, by the applicant, were sufficient to support the clinical indications appropriate to the smoking related disease of nicotine addiction but that the claims as currently proposed did not adequately reflect the medicinal use of nicotine supplements in those persons addicted to the alkaloid who suffer withdrawal symptoms when abstention from their normal source occurs.

The committee may wish to consider that a licence should be granted on condition that the applicant provides revisions to the terms of the proposed licence and its associated documents which satisfactorily address the following matters :

The proposed terms of the licence, to properly reflect the medical treatment of nicotine dependent persons, references to heavily dependent smokers should be deleted in the absence of substantial evidence to support the statement.

The dose and dosage schedule recommendations should be revised so as to provide more detailed dosing advice relative to the patients pre-existing tobacco usage. Full details of use should be stated in the section in dosage recommendations as cross-references to other non-licence documents are not sufficient.

The treatment period should be presented as a maximum of three months and not as currently recommended so as to minimise the incidence of substituted dependence.

The tapering of dose at the end of the treatment period should be described in more readily understandable terms.

The product should be specifically contraindicated in children and persons up to the age of 18 years.

Concomitant use of other licensed nicotine products should be proscribed.

The advice in respect of driving and operating machinery should clearly state that 'the nasal spray should not be used while driving or operating machinery as sneezing and watering eyes can contribute to accidents which may result in serious injury'.

A clearer description of the adverse events experienced by the majority of subjects at the initiation of treatment should be provided.

A clear statement should be introduced on the occurrence of substituted dependence.

17. ASSESSOR

[redacted]

December 1993

INDEX OF ATTACHMENTS