ACMD

Advisory Council on the Misuse of Drugs

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Karen Bradley MP
Minister for Preventing Abuse and Exploitation
Home Office
2 Marsham Street
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14 January 2016

Dear Minister,

Re: Further advice on the third generation synthetic cannabinoids: recommendations and addendum

On the 27 November 2014 the Advisory Council on the Misuse of Drugs (ACMD) provided advice to the then Minister for Crime Prevention on third generation synthetic cannabinoids.

The advice included an additional generic control drafted to address the wide range of 'third generation' synthetic cannabinoids then being seen. It was subsequently found that the scope of the proposed definition unintentionally covered two existing Class A drugs as well as zafirlukast, the active ingredient of the licensed medicinal product "Accolate".

On the 25 March 2015 the ACMD published an addendum, which recommended an amendment to the generic definition to exempt from the proposed generic definition:

- clonitazene and etonitazene; and,
- the medicine known as zafirlukast (cyclopentyl 3-{2-methoxy-4-[(2-methylphenylsulfonyl)carbamoyl]phenylmethyl}-1-methyl-1H-indol-5-ylcarbamate).

New synthetic cannabinoids

However, since March 2015 several new synthetic cannabinoids, which are outside the scope of the proposed generic definition in the ACMD report, have appeared on the market or reported in a patent.

Two of these, namely 1-(5-fluoropentyl)-*N*-(2-phenylpropan-2-yl)-1*H*-pyrrolo[2,3-b]pyridine-3-carboxamide (CUMYL-5F-P7AICA) and 1-(5-fluoropentyl)-*N*-(naphthalene-1-yl)-1*H*-pyrrolo[3,2-c]pyridine-3-carboxamide (5F-PCN) have pyrrolo[2,3-b]pyridine and pyrrolo[3,2-c]pyridine, respectively, as 'core structures', which are not included in the proposed generic definition.

Another two new synthetic cannabinoids, namely (1-(5-fluoropentyl)-1*H*-indol-3-yl)(pyrrolidin-1-yl)methanone (5F-PY-PICA) and (1-(5-fluoropentyl)-1*H*-indazol-3-yl)(pyrrolidin-1-yl)methanone (5F-PY-PINACA) have the pyrrolidinyl group as a 'secondary structure', which is not included within the proposed generic definition, and another new synthetic cannabinoid, 1-pentyl-*N*-(4-phenyl-tetrahydropyran-4-yl)-1*H*-indole-3-carboxamide (SGT-240), has a tetrahydropyranyl secondary structure, which is not included within the proposed generic definition. Furthermore, it is likely that new synthetic cannabinoids may be produced with a piperidinyl or morpholinyl group as the 'secondary structure' as these are closely related to the pyrrolidinyl group.

Medicinal products within scope

Several medicines and compounds of interest to the pharmaceutical industry have been identified as having structural features which can be interpreted as falling within the scope of the proposed generic control. Ten of these, including zafirlukast mentioned in the previous addendum, are available in medicinal products approved for use in the UK or elsewhere within the EU.

Table 1: Medicines and potential medicines to be excluded from control

Name	Pharmacological activity	Trade Names in UK
Acemetacin	Anti-inflammatory	Emflex
Atorvastatin	Statin	Lipitor
Bazedoxifene	Selective estrogen receptor modulator	Germany, Lithuania, Sweden, Croatia and Israel (PO) only
Indometacin	Anti-inflammatory	Indocid, Indolar
Losartan	Angiotensin II receptor antagonist for hypertension	Cozaar
Olmesartan	Anti-hypertensive agent	Olmetec, Sevikar
Proglumetacin	Anti-inflammatory	Available in several countries e.g. Proxil (Italy) but not in the UK
Telmisartan	Anti-hypertensive agent	Actelsor, Micardis
Viminol	Analgesic	Dividol (Brazil and Italy)
Zafirlukast	Anti-asthmatic	Accolate

Recommendations and addendum

The ACMD recommends that:

1. the ‘core structures’ pyrrolo[2,3-b]pyridine and pyrrolo[3,2-c]pyridine are added to sub-paragraph (i) of the proposed generic definition.
2. the ‘secondary structures’, pyrrolidinyl, piperidinyl, morpholinyl and tetrahydropyranyl, are added to sub-paragraph (iv) of the proposed generic definition.
3. the ten compounds unintentionally covered by the generic definition proposed in the original report are listed by name as exempted from control under the Misuse of Drugs Act 1971. These are: *acemetacin, atorvastatin, bazedoxifene, indometacin, losartan, olmesartan, proglumetacin, telmisartan, viminol and zafirlukast*.

Taking into account the above three recommendations, the ACMD recommends the following revisions to the original report:

Revised paragraph 8.1

“Any compound (not being *clonitazene, etonitazene, acemetacin, atorvastatin, bazedoxifene, indometacin, losartan, olmesartan, proglumetacin, telmisartan, viminol and zafirlukast*) or a compound for the time being specified in subparagraph (c) above) structurally related to 1-pentyl-3-(1-naphthoyl)indole (JWH-018), in that the four sub-structures, that is to say the indole ring, the pentyl substituent, the methanone linking group and the naphthyl ring, are linked together in a similar manner, whether or not any of the sub-structures have been modified, and whether or not substituted in any of the linked sub-structures with one or more univalent substituents and where the modifications of the sub-structures are limited to any of the following, that is to say:

(i) replacement of the indole ring with indane, indene, indazole, pyrrole, pyrazole, imidazole, benzimidazole, pyrrolo[2,3-b]pyridine, pyrrolo[3,2-c]pyridine or pyrazolo[3,4-b]pyridine;

(ii) replacement of the pentyl substituent with alkyl, alkenyl, benzyl, cycloalkylmethyl, cycloalkylethyl, (*N*-methylpiperidin-2-yl)methyl, 2-(4-morpholinyl)ethyl or (tetrahydropyran-4-yl)methyl;

(iii) replacement of the methanone linking group with an ethanone, carboxamide, carboxylate, methylene bridge or methine group;

(iv) replacement of the 1-naphthyl ring with 2-naphthyl, phenyl, benzyl, adamantyl, cycloalkyl, cycloalkylmethyl, cycloalkylethyl, bicyclo[2.2.1]heptanyl, 1,2,3,4-tetrahydronaphthyl, quinolinyl, isoquinolinyl, 1-amino-1-oxopropan-2-yl, 1-hydroxy-1-oxopropan-2-yl, piperidinyl, morpholinyl, pyrrolidinyl, tetrahydropyranyl or piperazinyl.”

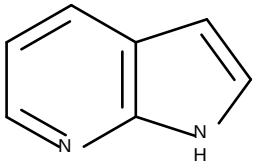
Revised paragraph 9.1

“The existing generic definitions are now well established and familiar to those who need to refer to the Misuse of Drugs Act and therefore the preferred option would be to add to the existing legislation rather than replace or modify it. The proposed

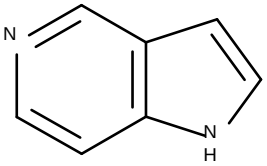
generic definition therefore includes an exception for those synthetic cannabinoids already controlled by the existing generic definition; together with two compounds clonitazene and etonitazene, which fall within the proposed generic definition but are already Class A controlled drugs, and several other compounds, namely; *acemetacin, atorvastatin, bazedoxifene, indometacin, losartan, olmesartan, proglumetacin, telmisartan, viminol and zafirlukast*.

This effectively excludes from control a number of compounds that have medicinal uses, namely; *acemetacin, atorvastatin, bazedoxifene, indometacin, losartan, olmesartan, proglumetacin, telmisartan, viminol and zafirlukast*.

Revision of Annex 1: The following core structures are added to Figure 1

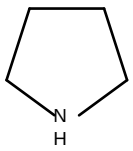


pyrrolo[2,3-b]pyridine

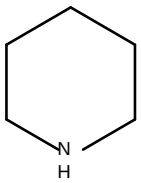


pyrrolo[3,2-c]pyridine

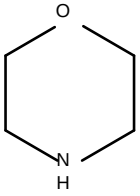
Revision of Annex 1: The following secondary structures are added to Figure 2



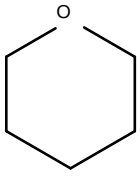
pyrrolidinyl



piperidinyl



morpholinyl



tetrahydropyranyl

The ACMD will continue to monitor the situation in regards to these substances.

Yours sincerely,

Professor Les Iversen

Chair of the ACMD