In the CLH dossier for Clomazone (September 2018) a classification regarding adverse effects on development "Repr. 1B, H360D May damage the unborn child" is proposed (page 87-88) based on skeletal findings in the rat with supporting evidence of skeletal findings in the rabbit. The main concern related to the Wistar rat study (2002) in which skeletal malformations of arthrogryposis or malformed fore- and hindlimbs were observed.

In the table below the incidence of major external and skeletal malformations are reported.

Parameters	**Doses [mg/kg bw/d]**			
	Control	250	500	750
Major external malformations (%)				
Number of foetuses examined	265	254	260	204
Forelimbs flexed at wrist	0.0	0.0	0.0	0.5[a] RE2792 n=1
Anasarca	0.0	0.0	0.4@ RE2750 n=1	0.5 RE2771 n=1
Major skeletal malformations (%)				
Number of foetuses examined	132	127	130	102
Multiple malformations[b]	0.0	0.0	0.8@ RE2750 n=1	0.0
Arthrogryposis	0.0	0.0	1.5 RE2751 n=1 RE2752 n=1	6.9** RE2789 n=1 RE2790 n=1 RE2794 n=3 RE2795 n=2
Forelimbs malformed	0.0	0.0	0.0	1.0 RE2797 n=1

[a] recorded as forelimb flexed in report summary data, however recorded as arthrogryposis in individual litter data; [b] Delayed skeletal ossification of skull bones, malformed forelimb with radius ulna bent, hind limb malformed with femur absent, tibia hypoplastic and malformed and fibula absent.
@ same fetus
** statistically significantly different
RExxxx = dam/litter no.; n = number of foetuses with the finding in the litter

For the litter for which forelimbs flexed at wrist/arthrogryposis was recorded during the external examinations, no skeletal malformations were recorded. In addition, for litters for which arthrogryposis or forelimbs malformed were recorded, no external malformations were recorded. This discrepancy in recording of these findings (external vs skeletal) questions whether the skeletal observations are real or artefacts of skeletal processing of the foetuses. Since arthrogryposis develops *in utero*, the contractures are present at birth and thus should have been observed at the external examination. Since the arthrogryposis was recorded in a higher incidence at the skeletal examinations it is more likely that these observations are artefacts resultant from inadequate foetal processing procedures. It has been reported in literature that artefacts resulting from less than optimal foetal processing procedures can occur and can lead to misidentification as malformations by inexperienced investigators (Principles and methods of toxicology 5th edition, Edited by Wallace Hayes, p1681).

In addition, there was some concern expressed in the CLH dossier regarding the developmental toxicity study in the rabbit (2002) for the incidence of malformations related to arthrogryposis. The

incidence of major malformations related to arthrogryposis are reported in the table below for the dose range finding element of the study.

Parameters	**Doses [mg/kg bw/d]**				
	Control	100	500	750	1000
Major external malformations (%)					
Number of foetuses examined	49	60	48	34	12
Arthrogryposis	8.2	0	0	0	0

In the main developmental toxicity study in the rabbit the following malformations related to arthrogryposis were recorded.

Parameters	**Doses [mg/kg bw/d]**			
	Control	150	350	700
Major external malformations (%)				
Number of foetuses examined	157	158	138	137
Forelimbs flexed at wrist	0.0	0.0	0.0	0.7 Rb4173 n=1
Multiple malformations	0.0	0.0	0.0	0.7 Rb4174 n=1
Major skeletal malformations (%)				
Number of foetuses examined	157	157	137	135
Hind limb (Rt/Lt/B) (+++) flexed at wrist	0.0	0.0	0.0	0.74@ Rb4174 n=1
Fore limb (Rt/Lt/B) (+++) flexed at wrist	0.0	0.0	0.0	0.74@ Rb4174 n=1

@= same fetus;
Rbxxxx = dam/litter no.; n = number of foetuses with the finding recorded in the litter;
+++=severe; Rt= right; Lt=left; B= both

The malformations related to arthrogryposis in the rabbit study fell within the historical control data of the period the study was conducted in the laboratory (max. incidence 3.2%). In addition, in the dose range finder with pregnant rabbits the incidence of arthrogryposis in the control group was 8.2% whereas no incidence of arthrogryposis was recorded in the treated groups. This clearly demonstrates that the incidence of fore- and hindlimbs flexed at wrist noted in the main study falls within the normal background incidence in this laboratory and is thus not treatment related.
Finally, a new previously not submitted developmental toxicity study in the Wistar rat was conducted (2019), in this study all foetuses were examined for morphological changes (external, visceral and skeletal) with no skeletal malformation related to arthrogryposis recorded. There were no treatment related effects on the incidences of supernumerary ribs, which are a sensitive indicator of an effect on the skeleton. In addition, there was no dose-related effect on ossification. These observations support the lack of an overall effect of clomazone on the developing skeleton following in-utero exposure.

In conclusion

It is ADAMA's position that a developmental toxicity classification is not warranted for clomazone for the following reasons:

- Arthrogryposis was only recorded in one of the three developmental toxicity studies in the rat.
    - One of these studies is a modern (2019) study in the same rat strain:
        - no external, visceral or skeletal foetal malformations or variations related to treatment were recorded
        - no indication of any increase in limb flexures (or arthrogryposis) were recorded.
    - If the skeletal findings in the one rat study were true findings, a similar pattern of effects should have been observed in all rat studies during both external and skeletal examination. Since this is not the case it is more probable that these findings are artefacts of foetal processing and not a true indication of a developmental effect of clomazone.
- The incidence of skeletal malformation related to arthrogryposis in the rabbit study fell within the normal background incidence of the laboratory.

Based on the weight of evidence presented, it is ADAMA's position that a developmental toxicity classification for Clomazone is not warranted.